Dearomatization applications of I(III) reagents and some unusual reactivity amongst resorcinol derived cyclohexadienones

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Abstract

The oxidative dearomatization of resorcinol derivatives, which are outfitted with a lactic acid derived chiral tether, and mitigated by hypervalent iodine derivatives of PhIO, affords stable chiral cyclohexadienones as useful building blocks for the construction of many highly functionalized chiral six and seven-membered ring systems. Herein, we report a multitude of remarkable and unexpected diastereoselective transformations stemming from these cyclohexadienone adducts.

Keywords

Dearomatization; Cyclohexadienone; Hypervalent iodine; Lactone; Vinylogous ester

1. Introduction

Despite many advances in asymmetric organic reaction processes, only a handful of chemical methods have emerged to provide enantiomerically enriched cyclohexadienones.[1] Few are catalytic. None are general. This is surprising because chiral cyclohexadienones offer attractive entry points to a number of complex non-racemic natural products. One needs to look no further than the early racemic syntheses of ryanodol, calicheamicinone, and ovalicin to be seduced by the utility of chiral cyclohexadienones. However, after reflecting and studying the processes that deliver these building blocks, we have come to appreciate the thorny issues of product stability and utility, which have prevented real progress. Any new dearomatization process should be judged just as much, if not more so, in these realms as in their overall diastereomeric or enantiomeric selectivity.

Diastereoselective dearomatization processes are inherently useful. In total syntheses of epoxysorbicillinol,[2] bisorbicillinol,[2] rishirilide,[3] and the cleroindicins,[4] as well as for other putative natural products,[5] we have confronted the issues of cyclohexadienone stability and subsequent utility head-on. Herein, we recount this diastereoselective dearomatization process, and report for the first time some of the remarkable reactivity we have observed amongst the resulting cyclohexadienone products.

2. The plan

Early on we speculated that a catalytic enantioselective method offered limited synthetic potential because its efficient use would be restricted by cyclohexadienone reactivity to circumstances where the target molecule contained a single stereocenter.[1] Therefore, our formulative ideas centered upon developing more utilitarian diastereoselective

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dearomatization processes.[6] We imagined some hypervalent I[(III)] reagent prompted oxidative dearomatization involving an unprecedented *ortho*-cyclization of a lactic acid derived tether should produce a family of sturdy cyclohexadienones capable of further regioselective and diastereoselective reactions.[7] Low yields (<70%) have long plagued the synthesis of cyclohexadienones. This stems from the reactivity of the reaction intermediates and the respective products. A workaround solution, which we were resolved to not use, has been the deployment of the oxidative dearomatization at a very early stage, when starting material is overly abundant, or very near the end, when the target compound can be easily reached. However, these solutions fail to capitalize on the malleability intrinsic to the cyclohexadienones product themselves. Fortunately, widespread use of hypervalent iodine oxidants,[8] particularly I[(III)] derivatives of iodosyl benzene (Ph–I=O),[9] have supplanted Pb[(IV)], Tl[(III)], and DDQ as oxidants. These hypervalent iodine reagents have led to improved yields, because these non-toxic I[(III)] reagents rarely participate in undesirable side-reactions with the intermediate phenonoxonium cation.[10]

We anticipated that the δ-lactone formed by our proposed oxidation would further stabilize the cyclohexadienone so that the enone, vinylogous ester, and ketone functionality could be manipulated in both chemoselective and stereoselective manners to address a number of natural products, in spite of the inescapable fact that the cyclohexadienone product would display five trigonal sp^2 carbon atoms. We therefore set out to build several of these scaffolds so that we might determine their subsequent reactivity, which we expected to be nucleus dependent. For example, *o*-quinol derivatives are susceptible to dimerization,[1b,d] whereas their *p*-quinol counterparts succumb to single electron transfer reduction and rearomatization.[11] While none of these issues can be avoided altogether, we imagined that some electronic and structural features could be introduced into the phenol and tether functionalities to dissuade some of undesired reactivities in the resulting cyclohexadienone adduct. An added benefit of our plan was that the oxygen atom, which would be installed during the dearomatization reaction, would be already protected. This increased the efficiency of any future synthetic plans by expanding the repertoire of accessible chemical transformations and obviating the need for subsequent hydroxyl protection.

3. Diastereoselective dearomatization with I[(III)] reagents; the affects of reaction conditions and substrate substituents on the overall yield and diastereoselectivity

Our studies have principally utilized two 2,4-dihydroxybenzaldehydes **1** (R′=–Me, –Br, Scheme 1). Some time ago, we reported a method for the straightforward conversion of these kinds of aldehydes into their corresponding 2-bromo- and 2-methyl-resorcinol derivatives **2** so as to display differing 4-alkyl substituents (**a**–**g**).[12] Before the development of our mild process, which involves *o*-quinone methide (*o*-QM) generation and consumption, these types of *mono*-protected 4-alkyl resorcinols were relatively inaccessible. The unprotected phenol product participates in an S_N2 reaction under Mitsunobu conditions with the secondary alcohol within various amides **3**, which are derived from (*S*)-methyl lactate.[13] Subsequent Boc deprotection with $ZnBr_2$ in CH_3NO_2 or in situ with aqueous LiOH at the conclusion of the Mitsunobu reaction affords the respective non-racemic mono-'protected' resorcinols **4** with enantiomeric excess of greater than 99%, demonstrated by chiral GC comparison of a derivative to a racemic standard.[6a]

Oxidation of these substrates using various PhI[(III)] species afford the corresponding lactones **5** as the major product (dr>12:1). In some instances, where the R″ substituent is fairly small (R″=–H), a minor amount (<7%) of the lactones **6** can be observed. However, this unwanted diastereomer is easily removed by column chromatography and it can even be re-introduced

into the synthetic stream by formation of the corresponding Weinreb amide followed by the appropriate reduction. Given the structure of the major product, we speculate that it arises from the compact, dipole stabilized transition-state. From this transition-state, the Me– of the lactate residue, and the $R''CH_2$– substituent emerge on the same face (*syn*) with respect to the newly forming 1,4-di-oxygenated ring. On the other hand, for the minor diastereomer **6**, the Me– and the $R''CH_2$– substituent emerge on the opposite face (*anti*). The X-ray crystal structures for **5a** and *ent*-**5a** have been previously reported.[4]

After much experimentation with the oxidative dearomatization of resorcinol 4d (R''=–$(CH_2)_2Ph$), which can undergo either *ipso* or *ortho*-cyclization (Scheme 1, inset shows the *ipso* product), we believe that we have successfully ascertained the optimum combination of reagents and substituents for the formation of the desired 1,4-dioxan-2-one scaffold 5.[3] Dilute conditions (0.05 M) and very polar solvents, particularly nitromethane (CH_3NO_2), proved best in most instances. A bromine or alkyl substituent at the 2-position of the resorcinol also appeared to facilitate the dearomatization process, and increase the diastereoselectivity. Remarkably, the lactate tether motif not only resulted in diastereoselection, it also improved yields and it provided a more stable cyclohexadienone adduct than the corresponding glycolate derived tethers. In addition, we found that the transformation can be carried out at much higher concentrations (0.3 M) in methylene chloride when the oxidation is carried out with either (1.1 equiv PhIO, 0.1 equiv TMSOTf) or (1.1 equiv PhIO and 1.1 equiv TfOH).[3,5] These oxidants, which are generated in situ, prevent any undesired participation of the ligand from the hypervalent iodine species with the intermediate phenoxonium cation.[14]

4. Some surprising reactivity differences amongst epimeric chiral cyclohexadienone adducts

The reactivity of the chiral cyclohexadienones **5** was next studied. Remarkably, all attempts to epoxidize cyclohexadienones resembling **5** under standard basic conditions failed.[15] In our experience, we found that as long as the tertiary alcohol is protected, then the resorcinol derived cyclohexadienones are quite stubborn toward epoxidation.[6] On the other hand, cyclohexadienones derived from phenols usually undergo epoxidation, even if their tertiary alcohol is protected.[16] The conditions we used for the attempted epoxidation, however, resulted in formation of the *ent*-**6** epimer. Indeed, independent treatment of the *syn*-δ-lactone **5a** (0.04 M in THF, 1.0 equiv DBU) caused rapid epimerization of the tether methyl residue to produce, upon quenching with silica gel, the corresponding *anti*-δ-lactone *ent*-**6a** (Scheme 2). We speculate the axial hydrogen atom is unusually acidic because of the attached vinylogous ester oxygen atom and its zwitterionic nature. Moreover, in the product **6a**, both of the sp^3 substituents in the 1,4-dioxan-2-one reside in a thermodynamically preferred *anti* 1,4-diaxial orientation. This *anti*-arrangement thwarts further access to the lactone carbonyl and many of the reactions that will be subsequently described (Scheme 6) for type **5**-system do not necessarily apply to the corresponding **6**-system. For example, compounds **6a,b** are a great deal less reactive with aluminum amides than their corresponding diastereomer **5a,b**. The relative and absolute stereochemistry of the two pyrrolidine products have been confirmed by X-ray analysis. In the case of the cyclohexadienone **7b**, the amide carbonyl is positioned in an eight-membered ring so as to form a hydrogen bond with the neighboring tertiary alcohol. In the cyclohexadienone **8b**, however, the carbonyl turns away from the tertiary alcohol. Again, this minor structural difference profoundly influences the subsequent chemistry. The enone **8b** smoothly undergoes *syn* selective anionic epoxidation (*t*-BuOOH, DBU), whereas the enone **7b** proves unreactive.

5. Remarkable electrocylization discovered

Even more interesting is the stereospecific electrocyclization that we observe upon treatment of the lactone **5** (0.1 M in THF) with $BnN^+Me_4^-OH$ or DBU. We postulated this reaction, which resembles a Favorskii rearrangement, proceeds through the anion shown to afford the γ-lactone **9** (Scheme 3). Again, the transformation is somewhat structure dependant. In the case of **5b**, where $[R''=-(CH_2)_5CH_3]$, the rearrangement product (R**=H) emerges quite cleanly (>85% yield). However, when $R''=-H$ as in **5a**, compound **9** emerges (R**=–H), along with a dimeric product where the tertiary alcohol has participated in a stereoselective 1,4-addition with the enone of the rearrangement product (1:3 ratio, monomer–dimer). Coincidently, this rearrangement does not readily occur with either the thermodynamic diastereomer **6b**, or the corresponding lactones displaying a glycolate derived tether (not shown), suggesting that the release of steric strain may play a role in the transformation. Our observation of this rearrangement in other cores, such as compound **10** and **18a**, which converts to **11** with a variety of bases,[17] leads us to believe that neither an electron deficient R' residue nor an enone are critical for this rearrangement process. However, the vinylogous ester and the *syn* configured 1,4-dioxan-2-one seem to be essential motifs.

6. Functional groups interconversion involving the lactone and vinylogous ester moieties

Owing to the conjoined 1,4-dioxan-2-one and vinylogous ester, compound **5** undergoes many other unusual functional group interconversions, several of which prove diastereoselective. Some time ago, we found that the glycolate lactone derivatives corresponding to **5** (not shown) undergo saponification and diastereoselective lactonization to afford a spirolactone.[2] Further saponification cleaves the spirolactone to reveal the carbonyl moiety that was previously masked as the vinylogous ester and thereby removes the tether. In the case of the lactic acid cyclohexadienone derivatives, such as **5**, however, the reaction is less synthetically useful. Saponification and subsequent lactonization now proceeds to a mixture of γ-spirolactone adducts (**14** and **15**) possessing dissimilar reactivity (2:1 ratio, 95% overall yield). Compound **14**, for example, undergoes an E2 elimination rather than saponification upon treatment with aqueous base to return the starting lactone **5**, whereas compound **15** converts under similar conditions into the corresponding β-diketone (not shown). Compound **5** does, however, undergo a highly diastereoselective transformation to afford the lactam **12** upon the addition of a primary amine (74% yield for **12a**, Scheme 4). Amines $R'''=-Bn$ and –Bu have both been tested.[15] The resulting spirocyclic lactam **12** forms as a single diastereomer and undergoes further stereoselective epoxidation to produce the anticipated *syn*-epoxy-alcohol **13** (85% yield). X-ray analysis of **13** has secured the stereochemistry of the cyclization despite some variability throughout the lipophyllic side chain. Yields are lower for cyclohexadienones when the R'=alkyl residues (**12f**) as opposed to R'=–Br; it therefore appears that this lactamization is facilitated, at least some degree, by an electron deficient R' residue.

7. Reactions of the cyclohexadienone scaffold 5

Because of a pseudo equatorial arrangement of the C–O bond on the cyclohexadienone, as opposed to a pseudo axial orientation, the bicyclic compound **5** enjoys enhanced chemical and thermal stability as compared to a rudimentary *p*-quinol acetate cyclohexa-2,5-dienone adduct. Compound **5** is far less susceptible to single electron transfer and elimination. Moreover, because of the pseudo axial $–CH_2R''$ residue, many reactions of the bicyclic compound **5** prove stereoselective. For example, compound **5a** undergoes a selective [3+2] cycloaddition with diazomethane at 0 °C in diethyl ether to afford the tetrahydro-3*H*-

indazole **16a** (76% yield, Scheme 5).[18] On the other hand, the enone **5g** proceeds in a [4+2] cycloaddition at 155 °C in a sealed tube containing toluene and the masked Durst–Charlton dimethide[19] to afford the tricyclic ring system **17g** as a single diastereomer.[17] Type **5** enones can also participate in 1,4-conjugate additions. For example, addition of the magnesium enolate[20] to **5a** followed by decarboxylation results in the formation of the ester **18a**, which under basic conditions undergoes further rearrangement to afford **19a** as a single diastereomer. However, 1,4-conjugated addition of alkyl and vinyl cuprates is not as useful. In most instances the cyclohexadienone succumbs to single electron transfer and elimination to return an aromatic product (not shown). For example, addition of Stryker's reagent ($[Ph_3PCuH]_6$) to compound **5b** affords the anticipated reduced product **20b** (50% yield) along with about a 40% yield of the corresponding 2-(R)-(2-bromo-6-heptyl-3-hydroxyphenoxy)-propanoic acid (not shown). We therefore chose to next examine other potentially chemoselective and stereoselective reduction procedures to better understand and unleash the utility of this new chiral building block.

8. Reductions of the cyclohexadienone 5 and related scaffolds

Despite its structural enhancements and rigidity, type **5** cyclohexadienones still performed erratically in most transition metal mediated procedures. Thus, most hydrogenation conditions are accompanied with a fair amount of rearomatization.[6a] After considerable experimentation and newly found appreciation of Corey's ovalicin work, we chose to subject the enone **5** (0.07 M in CH_3NO_2) to a source of diimide, generated from potassium azodicarboxylate by the addition of 3 equiv of acetic acid.[21] The reduction smoothly afforded the vinylogous ester **20** (Scheme 6). With one of the double bonds removed, the vinylogous ester undergoes subsequent reduction with palladium/carbon and hydrogen to smoothly afford the ketone **21**. In addition, the bromine atom can be removed from **20** by standard conditions to afford its hydrido counterpart **21**. The vinylogous ester of **5** (0.1 M in toluene) at −78 °C succumbs to a diastereoselective reduction with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) (2.2 equiv) and L-Selectride (1.1 equiv) to afford the trans fused system **25** in 85% yield.[22] Lower yields are obtained in systems where R′=–Me residue **25f**, however the reaction is still quite useful. The bromide in scaffolds, such as **25a** can be removed by treatment with TMSI (2 equiv) or PPh_3 and methanol to furnish the enone **26** in 98% yield.[15] Hydrogenation of either compound **20** or **25** affords the expected ketone **21**. On the other hand, we found that addition of DIBAL (2 equiv) to **5a** (0.04 M in toluene at −78 °C) results in the lactol **22a** in 69% yield. Presumably, this transformation proceeds by sequential stereoselective reduction of the vinylogous ester, followed by the lactone. Surprisingly, the use of sodium borohydride (10 equiv) with **5a** (0.04 M in THF/H_2O at 0 °C) reduces the vinylogous ester, followed by 1,2-reduction of the enone to thereby afford compound **23a** in >75% yield. More remarkably still, compound **5a** (0.04 M in MeOH at −78 °C) in the presence of cerium trichloride (1.2 equiv) undergoes reduction of the lactone with sodium borohydride (2 equiv) to produce the lactol **24a**. This outcome was certainly not anticipated from Luche reduction conditions.

9. Other useful transformations of scaffolds derived from the cyclohexadienone 5

We have developed several methods for removal of the tether, that is, derived from methyl lactate and directs the stereochemical formation of the tertiary alcohol in the cyclohexa-2,5-dienone. The simplest is treatment of fused compounds, such as **21**, with KOTMS. Saponification of the lactone causes a ring flip and concomitant β-elimination of the lactate derived functionality.[6a] However, we have also developed processes that enables us to retain the oxygen atom by severing the C–O bond from both the lactone and its corresponding

hemiketal by formation of various hydrazone derivatives.[3,4] For example, treatment of **20a** (0.05 M in CH_2Cl_2 at 0 °C) with excess $Me_2AlNHNMe_2$ (3 equiv) affords a single vinylogous hydrazide. Subsequent silylation facilitating isolation as compound **27a**. Reduction of the enone carbonyl and lactone functionalities in **26a**, followed by allylic MnO_2 oxidation and treatment of the corresponding lactol with H_2NNMe_2 followed by TFA affords the diol **28a** by a similar C–O fragmentation mechanism.

The rigid enone **26** also participates in many other selective transformations. For example, it undergoes 1,4-addition of hydride mediated by rhodium to afford the corresponding silyl enol ether. Further epoxidation with DMDO affords compound **29b**. The enone in **26** also undergoes stereoselective cyclopropanation under Furukawa modified Simmons–Smith conditions to produce compound **30a** (Scheme 7). The conjugate addition of homo-allyl cuprate (0.04 M in THF at −78 °C) to afford **31a** is similarly diastereoselective. We speculated that the outstanding stereoselectivity in all of these reactions is due to the steric encumbrance of the angular $-CH_2R'''$ residue.

The equatorial bromide compound **25**, formed by L-Selectride reduction, also undergoes selective reactions. For example, bromination (1 equiv of Br_2; 1.5 equiv Et_3N) of enone **25** (0.05 M in CH_2Cl_2 at 0 °C) proceeds as expected to produce the vinyl bromide **32a**. On the other hand, treatment of **25a** (0.02 M in benzene at 80 °C) with AIBN and the allyl tin species shown (2 equiv) affords a single diastereomer of the unsaturated ester **33a** in greater than 80% yield.

The fully reduced scaffold **21** also undergoes some unexpectedly reactions. For example, in the presence of CH_2N_2, **21a** affords the spiroepoxide **34a**, rather than the intended ring expanded product (not shown). Surprisingly, migration proceeds in only one direction upon treatment of **21a** with *m*-CPBA, to afford the seven-membered lactone **35a** as a single regioisomer. This selective ring expansion further illustrates the remarkable and unexpected selectivity of these cylcohexadienones and their derivatives.

10. Conclusion

In closing, we believe that the dearomatization process, that is, mitigated by hypervalent iodine derivatives of PhIO, that afford chiral cyclohexadienones, such as **5** from the corresponding methyl lactate **3** and the resorcinol **2** compounds, displays tremendous potential. The cyclohexadienone **5**, that is, formed is a useful building block for both six and seven-membered rings as well as for acyclic arrays. Moreover, its epimer **6** is expected to afford a very different reactivity profile because its lactone carbonyl is better protected by the *anti*-3,5-alkyl substituents of the corresponding 1,4-dioxan-2-one. We therefore believe that the 5-pot protocol used to construct **5** in either optical antipode with various hypervalent iodine reagents might indeed find many good applications in future enantioselective syntheses.

11. Experimental procedures and spectral data for representative scaffolds 2–9, 11, 19–36

11.1. General techniques

In reactions, where water was not present as solvent, reagent, or by-product, vessels were flame-dried under a slow nitrogen flow. A slight positive pressure of dry nitrogen was maintained via rubber septum seal during the course of the reaction. Diethyl ether, tetrahydrofuran, benzene, and toluene were distilled from sodium and benzophenone. Dichloromethane and nitromethane were distilled from calcium hydride. ^{1}H NMR and [13]C

NMR spectra were recorded at 400 MHz and 100 MHz, respectively, and in CDCl$_3$ unless otherwise noted. Chromatography purification was performed using 40–63 μm silica gel.

11.2. Scaffold 4

To a stirred solution of triphenyl phosphine (6.49 g, 24.8 mmol) in THF (60 mL) at 0 °C was added diisopropyl azodicarboxylate (4.9 mL, 24.9 mmol), dropwise over 1 min. The resulting suspension was stirred from 0 °C to rt for 1 h. The mixture was re-cooled to 0 °C, and a solution of **3** (5.01 g, 16.5 mmol) in THF (40 mL) was added via a cannula, followed by a solution of **2a** (2.20 g, 16.5 mmol) in THF (25 mL). The reaction was stirred at 0 °C to rt for 12 h. It was concentrated under reduced pressure and crude residue was purified by column chromatography (20% EtOAc–hexanes) to afford a light yellow oil.

The above product was redissolved in CH$_3$NO$_2$ (125 mL) and ZnBr$_2$ (14.3 g, 63.4 mmol) was added. The reaction was stirred at rt for 5 h, then quenched with 1 M aq HCl and diluted with EtOAc. The organic layer was washed twice with 1 M citric acid, twice with deionized water, once with brine, and dried (Na$_2$SO$_4$). The mixture was filtered, concentrated, and the crude residue was purified by chromatography (30% EtOAc–hexanes) to afford **4a** as a white solid (4.11 g, 78% yield over two steps).

11.2.1. Compound 4a—^{1}H NMR δ (multiplicity, J (Hz), integration): 7.02 (d, 8.5, 1H), 6.74 (d, 8.4, 1H), 5.55 (s, 1H), 5.14 (d, 6.4, 1H), 3.59 (s, 3H), 3.23 (s, 3H), 2.28 (s, 3H), 1.55 (d, 6.6, 3H); ^{13}C NMR δ 172.4, 153.6, 152.1, 130.4, 124.7, 111.7, 105.9, 75.6, 61.6, 32.5, 18.1, 16.7; IR (thin film): 3242, 2934, 1651, 1423, 1177, 1076, 1038, 987 cm^{-1}; HRMS (ESI) calcd for C$_{12}$H$_{16}$NO$_4$BrNa$^+$: 340.0154, found 340.0159; mp=127–128 °C.

11.2.2. Compound 4f—Yield 75%. ^{1}H NMR (500 MHz) δ (multiplicity, J (Hz), integration): 6.83 (d, 8.2, 1H), 6.55 (d, 8.1, 1H), 5.54 (s, 1H), 4.88 (br q, 6.0, 1H), 3.49 (s, 3H), 3.2 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.49 (d, 6.6, 3H); ^{13}C NMR δ: 155.8, 153.4, 128.3, 122.9, 118.0, 111.0, 74.5, 61.5, 32.5, 18.2, 16.8, 10.1.

11.3. Scaffold 5

A solution of **4a** (0.363 g, 1.33 mmol) previously dried under vacuum (48 h at 0.07 mmHg), in CH$_3$NO$_2$ (12 mL) was cooled to 0 °C and [bis(trifluoroacetoxy)iodo]benzene (0.738 g, 1.72 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 15 min, and gradually turned light yellow. Deionized water (20 mL) was added followed by CH$_2$Cl$_2$ (20 mL) and it was stirred vigorously at 0 °C for 15 min. Upon initial addition of water the solution turned dark green, then faded to yellow after several minutes. The aqueous layer was extracted with CH$_2$Cl$_2$ four times and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated. The crude product was purified by flash chromatography (30% EtOAc–hexanes) to afford **5a** (0.224 g, 75% yield) as an off-white solid.

11.3.1. Compound 5a—^{1}H NMR δ (multiplicity, J (Hz), integration): 6.84 (d, 10.0, 1H), 6.36 (d, 10.0, 1H), 4.99 (q, 7.2, 1H), 1.88 (d, 7.2, 3H), 1.85 (s, 3H); ^{13}C NMR δ: 179.4, 166.5, 162.1, 143.1, 127.1, 107.0, 76.6, 74.4, 29.9, 19.5; IR (thin film): 2924, 1759, 1668, 1607, 1261, 1049 cm^{-1}; HRMS (EI) calcd for C$_{10}$H$_9$BrO$_4^+$ 271.9684, found 271.9689; mp=111–114 °C.

11.3.2. Compound 5b–d—See Ref. 6a.

11.3.3. Compound 5e—See Ref. 4.

11.3.4. Compound 5f—Yield 70%. ^{1}H NMR (500 MHz) δ (multiplicity, J (Hz), integration): 6.79 (d, 10.0, 1H), 6.24 (d, 10.0, 1H), 4.79 (q, 7.0, 1H), 1.87 (s, 3H), 1.81 (d, 7.0, 3H), 1.79 (s, 3H); ^{13}C NMR (125 MHz) δ: 186.5, 167.6, 160.0, 143.0, 128.1, 119.2, 75.5, 73.9, 29.4, 19.4, 7.6.

11.3.5. Compound 5g—See Ref. 3.

11.4. Scaffold 6

This minor diastereomer formed during the synthesis of **5** was isolated by chromatography (30% EtOAc–hexanes). Alternatively, *ent*-**6a** can be obtained from the following procedure: to a solution of **5a** (0.020 g, 0.073 mmol) in THF (2 mL) at 0 °C was added DBU (0.012 mL, 0.079 mmol). The reaction was stirred for 30 s, quenched with silica gel, and immediately concentrated under reduced pressure and purified by flash chromatography (30% EtOAc–hexanes) to afford *ent*-**6a** (0.018 g, 90% yield) as a light yellow oil.

11.4.1. Compound 6a—^{1}H NMR δ (multiplicity, J (Hz), integration): 6.80 (d, 10.0, 1H), 6.30 (d, 10.0, 1H), 5.20 (q, 6.5, 1H), 1.88 (s, 3H), 1.78 (d, 6.7, 3H); ^{13}C NMR δ: 179.2, 166.3, 162.6, 142.3, 126.7, 102.2, 77.0, 73.1, 27.0, 18.3; IR (thin film): 2923, 1767, 1666, 1603, 1286, 1248. 1055 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9BrO_4^+$: 271.9684, found: 271.9693.

11.5. Scaffold 7

To a solution of pyrrolidine (0.0034 mL, 0.041 mmol) in CH_2Cl_2 (0.5 mL) cooled to 0 °C was added AlMe$_3$ (0.0175 mL, 0.040 mmol, 2.3 M in hexanes), and the resulting solution was stirred at 0 °C for 25 min. A solution of dienenone **5a** (0.010 g, 0.036 mmol) in CH_2Cl_2 (0.5 mL) was added to the aluminum amide. The reaction was allowed to slowly warm to rt and was stirred for 2.5 h. It was quenched with aq 1 M Rochelle's salt, diluted with CH_2Cl_2, and stirred vigorously for 30 min. The aqueous layer was extracted four times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated, and the crude residue was purified by chromatography (40% EtOAc–hexanes) to afford **7a** as a light yellow oil (0.009 g, 75% yield).

11.5.1. Compound 7a—^{1}H NMR δ (multiplicity, J (Hz), integration): 6.84 (d, 9.9, 1H), 6.48 (s, 1H), 6.17 (d, 9.9, 1H), 6.08 (q, 6.7, 1H), 3.61–3.48 (m, 2H), 3.44–3.34 (m, 2H), 2.01 (quintet, 6.4, 2H), 1.87 (m, 6.4, 2H), 1.65 (d, 6.7, 3H), 1.58 (s, 3H); ^{13}C NMR δ: 181.2, 174.0, 170.1, 151.2, 123.6, 106.8, 75.5, 71.8, 46.9, 46.5, 27.0, 26.3, 23.9, 18.6; IR (thin film): 3252, 2977, 1664, 1630, 1583, 1458, 1186, 1026; HRMS (EI) calcd for $C_{14}H_{18}BrNO_4^+$: 343.0419, found: 343.0423.

11.5.2. Compound 7b—Yield 72%. ^{1}H NMR δ (multiplicity, J (Hz), integration): 6.76 (d, 10.1, 1H), 6.54 (s, 1H), 6.24 (d, 9.9, 1H), 6.03 (q, 6.8, 1H), 3.60–3.48 (m, 2H), 3.44–3.33 (m, 2H), 2.07–1.98 (m, 2H), 1.89–1.78 (m, 2H), 1.65 (d, 6.6, 3H), 1.30–1.00 (m, 12H), 0.87 (t, 6.8, 3H).

11.6. Scaffold 8

The procedure for scaffold **7** was used, except the reaction was allowed to stir for 6 h following the addition of dienone **6**. The reaction generally and gave slightly lower yields (68%).

11.6.1. Compound 8a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 6.84 (d, 10.0, 1H), 6.25 (d, 10.0, 1H), 5.66 (q, 6.8, 1H), 3.70–3.41 (m, 4H), 2.05 (quin, 6.7, 2H), 1.93 (quin, 6.7, 2H), 1.59 (s, 3H), 1.53 (d, 6.8, 3H).

11.6.2. Compound 8b—Yield 64%. ^{1}H NMR δ (multiplicity, *J* (Hz), integration): 6.77 (d, 9.8, 1H), 6.32 (d, 9.8, 1H), 6.19 (s, 1H), 5.54 (q, 6.83, 1H), 3.70–3.40 (m, 4H), 2.10–1.78 (m, 2H), 1.71–1.56 (m, 2H), 1.53 (d, 6.84, 3H), 1.34–1.17 (m, 12H), 0.86 (t, 6.83, 3H); IR (thin film): 3254, 2929, 1665, 1631, 1584, 1187 cm^{-1}.

11.7. Scaffold 9

To a solution of **5a** (0.020 g, 0.073 mmol) in THF (2 mL) at 0 °C was added DBU (0.012 mL, 0.079 mmol). The reaction was stirred for 30 min, then concentrated under reduced pressure and purified by flash chromatography (30% EtOAc–hexanes) to afford **9a** as a light yellow oil (0.017 g, 88% yield). For the synthesis of **9b**, BnNMe$_3$OH (40% wt in methanol, 1.0 equiv) was used instead of DBU, and the reaction was quenched with silica gel upon completion by TLC analysis.

11.7.1. Compound 9a (dimer)—^{1}H NMR (500 MHz) δ (multiplicity, *J* (Hz), integration): 6.80 (d, 10.3, 1H), 6.14 (d, 10.3, 1H), 5.15 (s, 1H), 4.24 (d, 10.1, 1H), 2.95 (d, 9.9, 1H), 2.65 (s, 1H), 1.93 (s, 3H), 1.81 (s, 3H), 1.79 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (125 MHz) δ: 188.0, 185.2, 173.6, 167.6, 152.6, 145.7, 130.2, 120.0, 89.2, 85.9, 85.5, 81.2, 74.4, 58.5, 55.3, 54.1, 32.2, 27.4, 20.9, 20.5; IR (thin film): 3464, 2925, 1794, 1757, 1695, 1380, 1120, 1072; HRMS (ESI) calcd for C$_{20}$H$_{18}$O$_8$Br$_2$Na$^+$: 566.9260, found: 566.9257.

11.7.2. Compound 9b (R**=H)—Yield 79%. ^{1}H NMR δ (multiplicity, *J* (Hz), integration): 7.2 (d, 10.0, 1H), 6.42 (d, 10.0, 1H), 2.61 (s, 1H), 2.21 (m, 1H), 2.0 (m, 1H), 1.98 (s, 3H), 1.38–1.17 (m, 10H), 0.86 (t, 6.8, 3H).

11.7.3. Compound 9c (R**=H)—Yield 80%. ^{1}H NMR δ (multiplicity, *J* (Hz), integration): 7.18 (d, 9.9, 1H), 6.44 (d, 9.9, 1H), 2.71 (s, 1H), 2.21 (dt, 4.5, 13.4, 1H), 2.01 (dt, 4.8, 12.4, 1H), 1.97 (s, 3H), 1.51 (sep, 6.7, 1H), 1.20 (m, 1H), 1.13 (m, 1H), 0.85 (t, 6.7, 6H).

11.8. Scaffold 11

To a solution of **10**[17] (0.012 g, 0.038 mmol) in THF (1 mL) was added KOTMS (0.0072 g, 0.057 mmol) and the resulting orange slurry was stirred for 25 min. The reaction was quenched with TFA (one drop), concentrated, and purified by column chromatography (20% EtOAc–hexanes) to afford **11** (0.009 g, 75% yield).

11.8.1. Compound 11—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 7.38 (dd, 9.8, 15.2, 1H), 6.41–6.21 (m, 3H), 3.96 (s, 1H), 2.05 (s, 3H), 1.90 (d, 6.8, 3H), 1.78 (s, 3H), 1.73 (s, 3H).

11.9. Scaffold 12

To a solution of **5a** (0.0500 g, 0.183 mmol) in CH$_2$Cl$_2$ (3 mL) cooled to 0 °C was added BnNH$_2$ (0.022 mL, 0.201 mmol). The solution was stirred at 0 °C to rt for 14 h, concentrated and purified by chromatography (40% EtOAc–hexanes) to afford **12a** (0.026 g, 74% yield based on consumed starting) and recovered **5a** (0.025 g, 50% recovery).

11.9.1. Compound 12a (R'''=Bn)—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 7.38 (m, 5H), 6.58 (d, 10.0, 1H), 6.18 (d, 10.0, 3H), 5.71 (s, 1H), 5.20 (d, 15.3, 1H), 4.77 (q, 6.8,

1H), 4.02 (d, 15.3, 1H), 1.46 (d, 6.8, 3H), 1.27 (s, 3H); ^{13}C NMR δ: 188.6, 175.6, 148.9, 137.5, 129.3, 128.7, 128.3, 127.6, 99.8, 75.8, 73.9, 60.9, 47.0, 23.6, 18.4; IR (thin film): 3380, 2924, 1697, 1095, 703; HRMS (ESI): calcd for $C_{17}H_{18}NO_4BrNa^+$: 402.0311, found: 402.0300.

11.9.2. Compound 12b (R‴=Bu)—This compound was characterized as is epoxide derivative **13b**.

Compound **12f** (R‴=Bn): 48% yield. ^{1}H NMR δ (multiplicity, *J* (Hz), integration): 7.44– 7.32 (m, 5H), 6.54 (d, 10.0, 1H), 6.06 (d, 10.0, 1H), 5.11 (d, 14.6, 1H), 4.54 (q, 6.8, 1H), 4.20 (d, 14.8, 1H), 3.52 (q, 7.0, 1H), 1.46 (d, 6.7, 3H), 1.24 (s, 3H), 1.01 (d, 6.8, 3H).

11.10. Scaffold 13

To a solution of **12b** (0.0047 g, 0.019 mmol) in CH_2Cl_2 (0.5 mL) was added *t*-BuOOH (0.0040 mL, 0.038 mmol) and DBU (cat.). The solution was stirred at rt for 45 h, concentrated, and purified by chromatography (40% EtOAc–hexanes) to afford **13b** (0.0041 g, 85% yield).

11.10.1. Compound 13b—^{1}H NMR (500 MHz) δ (multiplicity, *J* (Hz), integration): 4.67 (d, 1.7, 1H), 4.34 (q, 6.9, 1H), 3.75 (m, 1H), 3.63 (m, 2H), 3.55 (d, 3.7, 1H), 1.97 (m, 1H), 1.85 (m, 1H), 1.75 (m, 1H), 1.50–1.70 (m, 4H), 1.45–1.23 (m, 12H), 0.97 (t, 7.2, 3H), 0.90 (t, 6.8, 3H); ^{13}C NMR (125 MHz) δ: 197.6, 172.6, 102.9, 94.6, 91.7, 74.3, 54.4, 51.7, 42.3, 31.8, 31.6, 31.0, 29.2, 29.2, 22.8, 22.1, 20.6, 18.4, 14.3, 13.9; IR (thin film): 2930, 1718, 1413, 1374 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{32}NO_5Br^+$: 446.1542, found: 446.1559.

11.11. Scaffold 14,15

To a solution of **5a** (0.0730 g, 0.267 mmol) in THF was added LiOH (0.30 mL, 0.30 mmol, 1 M in H_2O). The solution was stirred for 10 min, then HCl (0.30 mL, 0.90 mmol, 3 M in H_2O) was added stirring was continued for 1 h. The THF was removed under reduced pressure; the aq solution was further diluted and extracted five times with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was a 2:1 mixture of **14a** and **15a** (0.0690 g, 95% NMR yield). Chromatography generally gave some separation and low isolated yields, however an analytically pure sample was obtained by flash chromatography (50% EtOAc–hexanes) to afford **14a** and a mixture of **14a** and **15a** (0.0140 g, 20% isolated yield).

11.11.1. Compound 14a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 6.87 (d, 10.3, 1H), 6.18 (d, 10.3, 1H), 5.01 (s, 1H), 4.90 (q, 6.8, 1H), 1.583 (s, 3H), 1.580 (d, 6.8, 1H); ^{13}C NMR δ: 187.0, 172.5, 152.2, 126.2, 111.1, 74.1, 73.3, 60.5, 22.6, 17.9; IR (thin film): 3461, 2925, 1803, 1697, 1271, 1204, 1003; HRMS (ESI) calcd for $C_{10}H_{11}O_5BrNa^+$ 312.9692, found 312.9694.

11.11.2. Compound 15a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 6.85 (d, 10.3, 1H), 6.20 (d, 10.3, 1H), 5.05 (s, 1H), 4.70 (q, 6.84, 1H), 1.60 (s, 3H), 1.59 (d, 6.8, 3H).

11.12. Scaffold 16

To a solution of **5a** (0.0050 g, 0.018 mmol) in ether (1 mL) at 0 °C was added diazomethane (0.27 M in Et_2O, 1.0 mL, 0.27 mmol) and the resulting solution was stirred for 12 h, gradually turning colorless. The reaction was concentrated and purified by crystallization from CH_2Cl_2–hexanes to afford **16a** (0.0043 g, 76% yield).

11.12.1. Compound 16a—^{1}H NMR (500 MHz) δ (multiplicity, J (Hz), integration): 5.86 (dd, 2.5, 9.4, 1H), 5.24 (dd, 9.5, 18.5, 1H), 5.12 (q, 7.4, 1H), 4.41 (ddd, 2.5, 9.7, 18.4, 1H), 2.98 (q, 9.4, 1H), 1.94 (s, 3H), 1.86 (d, 7.4, 3H); ^{13}C NMR (125 MHz) δ: 177.8, 165.6, 162.2, 103.6, 92.0, 81.0, 80.5, 72.8, 41.0, 33.4, 19.6; IR (thin film): 2988, 2942, 1759, 1672, 1597, 1273, 1211, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}N_2O_4NaBr^+$: 336.9800, found: 336.9798.

11.13. Scaffold 17

A mixture of dienone **5g** (0.080 g, 0.30 mmol), sulfone (0.87 g, 0.38 mmol), zinc oxide (0.081 g, 1.0 mmol), and K_2CO_3 (0.138 g, 1.00 mmol), in toluene (4 mL) was heated in a sealed tube to 155 °C for 8–10 h. The reaction was worked up with 2 M aq HCl and extracted with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated.

The crude material was taken up in $CHCl_3$ and treated with TFA (0.0093 mL, 0.125 mmol). The solution was stirred at rt for 4 h, concentrated and purified by chromatography (20% EtOAc–hexanes) to afford **17g** as a light yellow oil (0.067 g, 60% yield).

11.13.1. Compound 17g—^{1}H NMR δ (multiplicity, J (Hz), integration): 7.65 (d, 2.9, 1H), 7.20 (t, 7.7, 1H), 7.00 (d, 7.4, 1H), 6.95 (d, 7.4, 1H), 4.87 (q, 7.1, 1H), 3.88 (s, 3H), 3.46 (m, 1H), 3.27 (m, 1H), 2.67 (t, 16.6, 1H), 2.12 (m, 1H) 1.98 (s, 3H), 1.96 (m, 1H), 1.84 (d, 7.1, 3H), 1.53 (sep, 6.6, 1H), 0.88 (m, 6H).

11.14. Scaffold 18,19

To a cooled solution of *mono*-ethylmalonate (0.0043 mL, 0.036 mmol) in THF (0.5 mL) at 0 °C was added *t*-BuMgCl (0.83 M in THF, 0.089 mL, 0.072 mmol). The solution was stirred at 0 °C to rt for 10 h, and the residual solvent was removed by evaporation under a gentle flow of N_2. A solution of dienone **5a** (0.0050 g, 0.018 mmol) in DMF (0.5 mL) was added to the malonate salt and the solution was stirred at 60 °C for 2 h. The reaction was quenched with 1 M aq HCl and diluted with Et_2O. The organic layer was washed twice with water, once with brine, dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography (30% EtOAc–hexanes) to afford **19a** as a colorless oil (0.0039 g, 60% yield).

11.14.1. Compound 19a—^{1}H NMR δ (multiplicity, J (Hz), integration): 4.14 (q, 7.0, 1H), 3.13 (m, 1H), 2.95 (m, 3H), 2.74 (s, 1H), 2.57 (dd, 15.8, 5.4, 1H), 2.20 (dd, 15.8, 9.0, 1H), 1.95 (s, 3H), 1.82 (s, 3H).

11.15. Scaffold 20

To a solution of dienone **5a** (0.199 g, 0.729 mmol) in CH_3NO_2 (10 mL) at 0 °C was added potassium azodicarboxylate (1.706 g, 8.78 mmol). Acetic acid (1.50 mL, 26.2 mmol) was added dropwise via a syringe pump over 4 h while the temperature was maintained at 0 °C. The reaction mixture was immediately diluted with EtOAc, filtered through Celite, and washed successively with satd aq $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4), and concentrated. It was occasionally necessary to re-subject the crude material to additional potassium azodicarboxylate (1.137 g, 5.85 mmol) and acetic acid (1.00 mL, 17.5 mmol). The crude product was purified by crystallization from EtOAc–hexanes to afford **20a** (0.190 g, 95% yield). The diimide reduction proved superior over previously reported use of $[Ph_3PCuH]_6$ for **20b**,[17] and Rh–alumina hydrogenation to afford **20c**.[6a]

11.15.1. Compound 20a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 5.09 (q, 7.3, 1H), 2.88 (ddd, 2.4, 4.8, 17.5, 1H), 2.56 (ddd, 5.7, 8.3, 17.7, 1H), 2.40 (dt, 4.1, 13.1, 1H), 2.53 (ddd, 2.1, 5.6, 12.8, 1H), 1.87 (d, 7.3, 3H), 1.83 (s, 3H); ^{13}C NMR δ: 188.9, 166.7, 164.5, 105.6, 79.7, 73.4, 34.3, 34.0, 19.7; IR (thin film) 2941, 1751, 1670, 1600, 1274, 1188, 1038 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{11}BrO_4^+$: 273.9841, found: 273.9832; mp=116–118 °C.

11.16. Scaffold 21

To a solution of enone **20a** (0.057 g, 0.207 mmol) in EtOAc (3 mL) in 50 mL flask was added Pd/C (10%, 0.011 g, 0.010 mmol) followed by KOAc (0.034 g, 0.313 mmol). The flask was purged with H_2 for several minutes, then stirred under a H_2 balloon for 4 h. The reaction mixture was filtered through a pad of Celite, and concentrated. The crude material was purified by chromatography (30% EtOAc–hexanes) to afford **21a** as a colorless oil (0.040 g, 0.203 mmol, 98% yield).

11.16.1. Compound 21a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 4.46 (q, 7.0, 1H), 3.84 (dd, 10.2, 1H), 2.79 (ddd, 15.8, 5.6, 2.3, 1H), 2.56 (dd, 16.7, 5.1, 1H), 2.43 (dd, 13.1, 15.4, 1H), 2.38 (dd, 14.0, 7.3, 1H), 2.17 (ddd, 13.4, 8.8, 1.9, 1H), 1.93 (dd, 13.9, 5.6, 1H), 1.62 (s, 3H), 1.61 (d, 7.0, 3H); ^{13}C NMR δ: 205.14, 170.1, 81.63, 75.16, 73.15, 43.85, 37.74, 31.67, 18.59, 18.38; IR (thin film) 2988, 2943, 2880, 1731, 1373, 1257. 1124 cm^{-1}; HRMS (CI) calcd for $C_{10}H_{15}O_4^+$: 199.0970, found: 199.0968.

11.16.2. Compound 21c—Please see Ref. 6a.

11.17. Scaffold 22

To a solution of dienone **5a** (0.0500 g, 0.183 mmol) in toluene (5 mL) cooled to −78 °C was added DIBAL (1 M in hexanes, 0.366 mL, 0.366 mmol). The solution was stirred at −78 °C for 15 min. It was quenched with 1 M aq Rochelle's salt, diluted in EtOAc, quickly warmed to rt and stirred vigorously for 30 min. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (30% EtOAc–hexanes) to yield **22a** as a colorless oil (0.035 g, 0.127 mmol, 69% yield).

11.17.1. Compound 22a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 7.04 (d, 10.0, 1H), 6.05 (d, 10.1, 1H), 4.89 (t, 8.0, 1H), 4.41 (d, 12.4, 1H), 3.92 (d, 12.4 Hz, 1H), 3.46 (dq, 6.2, 8.2, 1H), 2.76 (d, 8.0, 1H), 1.56 (s, 3H), 1.39 (d, 6.2, 3H); ^{13}C NMR δ: 190.4, 153.6, 126.6, 94.0, 82.5, 78.7, 76.0, 51.7, 19.1, 16.7; IR (thin film) 3450, 2980, 2935, 1691, 1105, 1080 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}BrO_4Na^+$: 300.9868, found: 300.9879.

11.18. Scaffold 23

Dienone **5a** (0.021 g, 0.077 mmol) was dissolved in THF–H_2O (5/1, 1.8 mL) and cooled to 0 °C. $NaBH_4$ (0.0029 g, 0.77 mmol) was allowed to stand in air for several minutes until it appeared slightly moist, at which time it was added to the dienone solution. Addition of dry $NaBH_4$ generally resulted in a mixture of products, including over-reduction. The reaction was stirred for 5 min at 0 °C, quenched with saturated NH_4Cl, and diluted in EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude material was purified by flash chromatography (40% EtOAc–hexanes) to give **23a** as colorless oil (0.016 g, 0.059 mmol, 76% yield).

11.18.1. Compound 23a—^{1}H NMR (500 MHz) δ (multiplicity, J (Hz), integration): 5.90 (dd, 2.3, 10.2, 1H), 5.73 (dd, 2.7, 10.3, 1H), 4.65 (m, 1H), 4.49 (q, 7.0, 1H), 3.96 (dd, 8.0, 12.0, 1H), 3.82 (d, 12.0, 1H), 2.65 (d, 4.5, 1H), 1.66 (d, 7.0, 3H), 1.55 (s, 3H); ^{13}C NMR (125 MHz) δ: 170.1, 130.7, 128.8, 81.6, 75.6, 75.1, 67.5, 54.2, 24.2, 18.6; IR (thin film) 3435, 2986, 2938, 2872, 1744, 1275, 1227, 1047 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}BrO_4Na^+$: 298.9889, found: 298.9894.

11.19. Scaffold 24

A suspension of anhydrous $CeCl_3$ (0.010 g, 0.046 mmol) and MeOH (1 mL) was cooled to −78 °C. Dienone **5a** (0.01 g, 0.037 mmol) was added, followed by $NaBH_4$ (0.0018 g, 0.048 mmol). The temperature was maintained at −78 °C and additional $NaBH_4$ (0.0018 g, 0.048 mmol) was added every hour until the reaction was complete by TLC. The reaction was normally completed within 2–3 h. The reaction was quenched with satd aq NH_4Cl, and diluted in EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude material was purified by flash chromatography (30% EtOAc–hexanes) to give **24a** as colorless oil (0.009 g, 85% yield).

11.19.1. Compound 24a—^{1}H NMR (500 MHz) δ (multiplicity, J (Hz), integration): 6.82 (d, 9.9, 1H), 6.25 (d, 9.9, 1H), 5.19 (m, 1H), 4.01 (q, 6.5, 1H), 2.96 (s, 1H), 1.71 (s, 3H), 1.59 (d, 6.5, 3H); ^{13}C NMR (125 MHz. $CDCl_3$) δ: 180.6, 168.9, 147.0, 125.9, 105.5, 92.7, 80.0, 73.6, 27.2, 17.1; IR (thin film) 3398, 2986, 2935, 1659, 1591, 1027, 1055; HRMS (ESI) calcd for $C_{10}H_{11}BrO_4Na^+$: 296.9732, found: 296.9737.

11.20. Scaffold 25

A solution of BHT (1.88 g, 8.54 mmol) in toluene (15 mL) was cooled to 0 °C and $AlMe_3$ (25% in hexanes, 1.85 mL, 4.26 mmol) was added. The resulting mixture of MAD was stirred at 0 °C to rt for 1 h, then cooled to −78 °C. In a separate flask, dienone **5a** was dissolved in toluene (5 mL), and the solution was added via cannula to the MAD at −78 °C, immediately turning deep purple. The reaction was stirred for 5 min, then L-Selectride (1 M in THF, 2.1 mL, 2.1 mmol) was added and the solution was stirred for another 5 min at −78 °C. The reaction mixture was quenched with 1 M Rochelle's salt (10 mL), diluted with EtOAc (20 mL), and quickly warmed by hand to rt. It was stirred vigorously for 1 h. The aqueous layer was extracted with EtOAc four times and the combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by flash chromatography (100% hexanes to 30% EtOAc–hexanes) to give **25a** as white solid (0.410 g, 1.49 mmol, 77% yield).

11.20.1. Compound 25a—^{1}H NMR δ (multiplicity, J (Hz), integration): 7.08 (d, 10.2, 1H), 6.17 (d, J=10.0 Hz, 1H), 4.63 (q, 7.0, 1H), 4.50 (d, 11.9, 1H), 4.13 (d, 11.9, 1H), 1.69 (d, 7.0, 3H), 1.66 (s, 3H); ^{13}C NMR δ: 188.7, 168.9, 149.6, 127.6, 80.8, 79.8, 74.6, 50.4, 22.5, 18.4; IR (thin film) 2923, 1747, 1693, 1271, 1225, 1182, 1070 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{11}BrO_4Na^+$: 296.9732, found: 296.9737.

11.20.2. Compound 25b—Yield 85%. ^{1}H NMR δ (multiplicity, J (Hz), integration): 7.10 (d, 10.1, 1H), 6.18 (dd, 10.1, 0.8, 1H), 4.60 (q, 6.6, 1H), 4.58 (d, 11.8, 1H), 4.14 (d, 11.8, 1H), 2.13 (t, 9.8, 3H), 1.66 (d, 7.1, 3H), 1.4–1.2 (m, 11H), 0.87 (t, 6.9, 3H). ^{13}C NMR δ: 188.6, 169.1, 149.6, 127.9, 83.0, 80.5, 74.5, 50.0, 37.2, 31.8, 30.1, 29.1, 22.8, 22.7, 18.4, 14.2.

11.20.3. Compound 25e—See Ref. 4.

11.20.4. Compound 25f—Yield 62%. ^{1}H NMR (500 MHz) δ (multiplicity, J (Hz), integration): 6.96 (d, 10.1, 1H), 6.01 (d, 10.1, 1H), 4.52 (q, 7.0, 1H), 3.75 (d, 12.1, 1H), 2.41 (dq, 12.5, 6.4, 1H), 1.64 (d, 7.0, 3H), 1.63 (s, 3H), 1.31 (d, 6.7, 3H); ^{13}C NMR (125 MHz) δ: 197.8, 169.9, 148.7, 128.8, 81.0, 79.9, 74.3, 44.6, 22.1, 18.5, 11.1.

11.21. Scaffold 26

To a solution of bromide **25a** (0.230 g, 0.842 mmol) in CH_3CN (15 mL) was added a solution of NaI (0.379 g, 2.53 mmol) in CH_3CN (5 mL), followed by TMSCl (0.215 mL, 1.68 mmol). The resulting orange solution was stirred at rt for 3 h then quenched with saturated aq $Na_2S_2O_3$. The colorless solution was diluted with EtOAc, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude material was purified by flash chromatography (30% EtOAc–hexanes) to afford **26a** as a colorless oil (0.162 g, 98% yield).

11.21.1. Compound 26a—^{1}H NMR δ (multiplicity, J (Hz), integration): 7.01 (d, 10.0, 1H), 6.02 (d, 10.0, 1H), 4.54 (q, 7.0, 1H), 4.17 (dd, 5.6, 13.1, 1H), 2.91 (dd, 5.6, 17.5, 1H), 2.49 (dd, 13.1, 17.5, 1H), 1.61 (m, 6H); ^{13}C NMR δ 149.6, 129.3, 80.8, 74.6, 40.3, 21.7, 18.5; IR (thin film) 2981, 2934, 1747, 1688, 1273, 1111; HRMS (CI) calcd for $C_{10}H_{13}O_4^+$: 197.0813, found: 197.0810.

11.21.2. Compound 26b—Yield 98%. ^{1}H NMR (500 MHz) δ (multiplicity, J (Hz), integration): 7.03 (d, 10.1, 1H), 6.03 (dd, 10.1, 0.9, 1H), 4.52 (q, 7.1, 1H), 4.20 (dd, 12.9, 5.7, 1H), 2.89 (ddd, 17.5, 5.7, 0.9, 1H), 2.58 (dd, 17.5, 12.9, 1H), 2.03 (t, 12.3, 1H), 1.76 (t, 13.2, 1H), 1.61 (d, 6.9, 3H), 1.40–1.20 (m, 10H), 0.88 (t, 6.8, 3H); ^{13}C NMR (125 MHz. $CDCl_3$) δ: 195.1, 169.9, 149.6, 129.6, 82.8, 75.2, 73.9, 39.9, 36.3, 31.9, 30.2, 29.2, 22.9, 22.8, 18.5, 14.3.

11.22. Scaffold 27

A solution of N,N-dimethylhydrazine (0.021 mL, 0.27 mmol) in CH_2Cl_2 (1.0 mL) was cooled to 0 °C and AlMe$_3$ (25% in hexanes, 0.110 mL, 0.253 mmol) was added dropwise. The solution was stirred and allowed to slowly warm to rt for 1 h. The solution was cooled to 0 °C, and to it was added the vinylogous ester **20a** (0.023 g, 0.084 mmol) as a solution in CH_2Cl_2 (0.5 mL). The reaction was stirred from 0 °C to rt for 4 h. The reaction was quenched with 1 M aq Rochelle's salt, diluted with EtOAc and stirred vigorously for 1 h. The aqueous layer was extracted four times with EtOAc, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. To facilitate isolation, the product was derivatized as the silyl ether.

The crude product was dissolved in CH_2Cl_2 (1.5 mL) and Et$_3$N (0.105 mL, 0.753 mmol) was added, followed by TBSOTf (0.115 mL, 0.501 mmol). Stirring was continued at rt for 40 min, then the reaction was quenched with satd aq NaHCO$_3$ and diluted in CH_2Cl_2. The aqueous layer was extracted four times with CH_2Cl_2 and the combined organics were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (20% EtOAc–hexanes) to afford **27a** as a colorless oil (0.020 g, 64% yield over two steps).

11.22.1. Compound 27a—^{1}H NMR δ (multiplicity, J (Hz), integration): 5.70 (s, 1H), 2.66–2.57 (m, 1H), 2.32 (dt, 17.5, 4.9, 1H), 1.81 (m, 7H), 1.49–1.43 (m, 1H), 1.39 (s, 3H), 1.00 (s, 9H), 0.24 (s, 3H), 0.30 (s, 3H); ^{13}C NMR δ: 187.9, 159.5, 92.4, 75.9, 48.1, 36.8, 26.5, 25.7, 24.4, 19.0, −2.1, −3.1; IR (thin film) 2926, 2971, 2854, 1581, 1387 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{29}BrN_2O_2Si^+$: 399.1073, found: 399.1090.

11.23. Scaffold 28

To a solution of **26a** (0.098 g, 0.499 mmol) in toluene (7 mL) cooled to −78 °C was added DIBAL (1 M in hexanes, 2.50 mL, 2.50 mmol) and the solution was stirred for 1 h. The reaction mixture was quenched with 1 M aq Rochelle's salt, diluted with EtOAc, quickly warmed to rt and stirred vigorously for 45 min. The aqueous layer was extracted with EtOAc four times. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude reaction material was sufficiently pure for subsequent chemistry.

To a solution of the above crude product in CH_2Cl_2 (10 mL) was added active precipitated MnO_2 (1.063 g, 12.2 mmol) and the solution was stirred at rt for 16 h. The reaction mixture was filtered through Celite and concentrated. The crude material was sufficiently pure for subsequent chemistry.

To a solution of the crude reaction material in CH_2Cl_2 (5 mL) was added H_2NNMe_2 (0.025 mL, 0.549 mmol). The solution was stirred at rt for 4 h, and concentrated under reduced pressure to afford the hydrazone, which was taken on crude in the following sequence.

The hydrazone (0.064 g, 0.566 mmol) was dissolved in $CHCl_3$ (5 mL). TFA (five drops) was added and the reaction was stirred at rt for 9 h. It was concentrated and the residue was purified by chromatography (5% MeOH–CH_2Cl_2) to provide **28a** as a colorless oil (0.036 g, 51% yield over four steps).

11.23.1. Compound 28a—^{1}H NMR δ (multiplicity, J (Hz), integration): 6.85 (d, 10.1, 1H), 5.94 (d, 10.2, 1H), 4.14 (dd, 5.1, 12.1, 1H), 2.83 (dd, 5.1, 17.0, 1H), 2.45 (dd, 12.1, 16.9, 1H), 1.9 (br s, 2H), 1.43 (s, 3H); ^{13}C NMR δ: 197.5, 154.6, 128.4, 73.8, 73.4, 43.3, 20.7; IR (thin film) 3409, 2954, 2921, 1666, 1047 cm^{-1}; HRMS calcd for $C_7H_{11}O_3^+$: 143.0708, found: 143.0705.

11.24. Scaffold 29

To a solution of **26b** (57.9 mg, 0.207 mmol) in degassed benzene (4 mL, 0.05 M) was added triethylsilane (0.33 mL, 2.07 mmol) and RhCl(PPh_3)$_3$ (19.0 mg, 0.0207 mmol) and the solution was stirred for 2 h. The solvent was removed by evaporation under a gentle flow of N_2 and the residue was taken up in hexanes. The catalyst was removed by filtration through a cotton pad and the solution was concentrated under reduced pressure. The crude oil was dissolved in CH_2Cl_2 (0.5 mL) and cooled to 0 °C. A solution of DMDO (0.04 M in acetone, 3 mL, 0.62 mmol) was added and the reaction was stirred at 0 °C for 1 h. The reaction mixture was dried (Na_2SO_4) and concentrated. The residue was purified by alumina chromatography (5% EtOAc–pet. ether) to afford of **29b** (0.0598 g, 70% yield).

11.24.1. Compound 29b—^{1}H NMR δ (multiplicity, J (Hz), integration): 4.28 (q, 6.9, 1H), 3.62 (dd, 5.8, 11.1, 1H), 3.14 (dd, 1.1, 5.5, 1H), 2.59 (dd, 1H, 5.8, 14.1, 1H), 2.46 (dd, 1H, 5.7, 15.4, 1H), 2.08 (dd, 11.1, 14.1, 1H), 1.93 (t, 9.5, 3H), 1.79 (dd, 1.8, 15.4, 1H), 1.4–1.2 (m, 18H), 0.96 (m, 9H), 0.89 (t, 7.1, 3H), 0.63 (m, 6H).

11.25. Scaffold 30

To a solution of enone **26a** (0.0050 g, 0.025 mmol) in toluene (1.0 mL) at 0 °C was added Et_2Zn (1 M in hexanes, 0.052 mL, 0.052 mmol) followed by CH_2I_2 (0.0045 mL, 0.050 mmol). The reaction was stirred at 0 °C to rt for 40 h. Pyridine (0.050 mL) was added and the solution was stirred for 10 min, then diluted with EtOAc and worked up with H_2O. The aqueous layer was extracted four times with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by

chromatography (30% EtOAc–hexanes) to afford **30a** as a colorless oil (0.0038 g, 71% yield).

11.25.1. Compound 30a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 4.46 (q, 7.0, 1H), 4.44 (dd, 10.8, 7.2, 1H), 3.77 (d, 4.1, 1H), 3.49 (d, 4.2, 1H), 2.90 (dd, 19.4, 7.2, 3H), 2.29 (dd, 19.3, 10.8, 3H), 1.58 (d, 7.0, 3H), 1.29 (m, 2H).

11.26. Scaffold 31

Freshly prepared homoallylic magnesium bromide (0.153 mmol) in THF (0.5 mL) was added to CuBr · Me$_2$S (0.12 g, 0.058 mmol), instantly forming a dark purple solution. HMPA (0.054 mL, 0.31 mmol) was added to the cuprate and the solution was cooled to −78 °C. In a separate flask, enone **26a** (0.0080 g, 0.041 mmol) was dissolved in THF (0.5 mL) and TMSCl (0.032 mL, 0.25 mmol) was added. The enone solution was added via a cannula to the cuprate solution and the reaction was stirred at −78 °C for 1.5 h. Et$_3$N (0.035 mL, 0.25 mmol) was added to the solution, and it was warmed to rt, diluted with Et$_2$O, and worked up with H$_2$O. The organic layer washed twice with water, once with brine, dried (Na$_2$SO$_4$), and concentrated. It was purified by chromatography (20% EtOAc–hexanes) to afford **31a** (0.0080 g, 89% yield).

11.26.1. Compound 31a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 5.73 (m, 1H), 5.01 (m, 2H), 4.43 (q, 7.0, 1H), 3.99 (dd, 5.8, 12.6, 1H), 2.79 (dd, 5.8, 15.4, 1H), 2.54 (d, 4.3, 2H), 2.46 (dd, 12.5, 15.4, 1H), 2.16 (m, 2H), 1.96 (m, 2H), 1.68 (s, 3H), 1.60 (d, 7.0, 3H).

11.27. Scaffold 32

To a solution of **25a** (0.0740 g, 0.269 mmol) in CH$_2$Cl$_2$ (4.0 mL) at 0 °C was added a solution of Br$_2$ (0.043 g, 0.269 mmol) in CH$_2$Cl$_2$ (1.0 mL) dropwise over 1 h using a syringe pump. The solution was stirred for an additional 1 h and allowed to gradually warm to rt, as the solution turned from light orange to colorless. The solution was re-cooled to 0 °C and Et$_3$N was added (0.056 mL, 0.40 mmol). The reaction was stirred for an additional 30 min and quenched with 1 M aq HCl. The aqueous layer was extracted with CH$_2$Cl$_2$ four times. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated. The crude product was purified by chromatography (10% EtOAc–hexanes) to afford **32a** (0.053 g, 56% yield).

11.27.1. Compound 32a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 7.52 (s, 1H), 4.64 (q, 7.0, 1H), 4.58 (d, 12.0, 1H), 4.16 (d, 12.0, 1H), 1.68 (m, 6H).

11.28. Scaffold 33

To a solution of enone **25a** (0.0050 g, 0.018 mmol) and ethyl 2-((tributylstannyl)methyl)acrylate (0.015 g, 0.037 mmol) in benzene (1.0 mL) was added AIBN (0.00060 g, 3.6 μmol) and the mixture was heated to 80 °C for 12 h. The solvent was removed under reduced pressure and the residue was purified by chromatography (30% EtOAc–hexanes) to afford **34a** (0.0045 g, 81% yield).

11.28.1. Compound 33a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 6.96 (d, 10.2, 1H), 6.20 (d, 1.1, 1H), 6.00 (d, 10.2, 1H), 5.64 (d, 1.1, 1H), 4.36 (q, 7.0, 1H), 4.22 (m, 2H), 3.90 (d, 11.6, 1H), 3.01 (m, 1H), 2.74 (m, 2H), 1.61 (m, 6H), 1.32 (t, 7.2, 3H).

11.29. Scaffold 34

Compound **21a** (0.00236 g, 0.0119 mmol) was dissolved in a solution of CH$_2$N$_2$ (0.27 M in ether, 1 mL, 0.27 mmol). The mixture was stirred at 0 °C to rt for 4 h, or until the yellow

solution turned colorless. Additional CH_2N_2 solution (1 mL) was added and the process was repeated twice. After the third portion of CH_2N_2 had turned colorless, the solution was concentrated and the residue was purified by chromatography to afford **34a** as a colorless oil (0.00131 g, 52% yield).

11.29.1. Compound 34a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 4.45 (q, 7.0, 1H), 3.90 (dd, 12.4, 4.8, 1H), 2.71 (m, 2H), 1.96 (m, 4H), 1.56 (m, 5H), 1.46 (s, 3H); ^{13}C NMR (125 MHz) δ: 170.8, 82.6, 76.1, 73.9, 56.9, 52.6, 35.7, 33.0, 29.8, 18.7, 18.5.

11.30. Scaffold 35

To a solution of **21a** (0.00570 g, 0.0289 mmol) in CH_2Cl_2 (1.0 mL) was added *m*-CPBA (0.0200 g, 0.111 mmol) followed by $NaHCO_3$ (0.0045 g, 0.054 mmol). The solution was stirred at rt for 2 days. Additional *m*-CPBA (0.030 g, 0.174 mmol) and $NaHCO_3$ (0.0060 g, 0.072 mmol) were added and stirring was continued for 24 h. The reaction was quenched with satd aq $Na_2S_2O_3$ and diluted with CH_2Cl_2. The organic layer was washed with aq $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 four times. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude material was purified by chromatography (40% EtOAc–hexanes) to afford **35a** (0.00401 g, 65% yield).

11.30.1. Compound 35a—^{1}H NMR δ (multiplicity, *J* (Hz), integration): 4.47 (q, 7.0, 1H), 4.35 (ddd, 2.6, 5.1, 13.9, 1H), 4.18 (dd, 10.7, 13.8, 1H), 3.83 (5.1, 8.6, 1H), 2.85 (m, 2H), 2.17 (m, 2H), 1.58 (m, 6H); ^{13}C NMR δ: 170.2, 169.4, 83.5, 77.4, 73.9, 63.9, 38.8, 36.7, 19.1, 18.3; IR (thin film): 2923, 1734, 1286, 1258, 1143, 1086 cm^{-1}; HRMS (EI): calcd for $C_{10}H_{15}O_5^+$: 215.0919, found: 215.0914.

Acknowledgments

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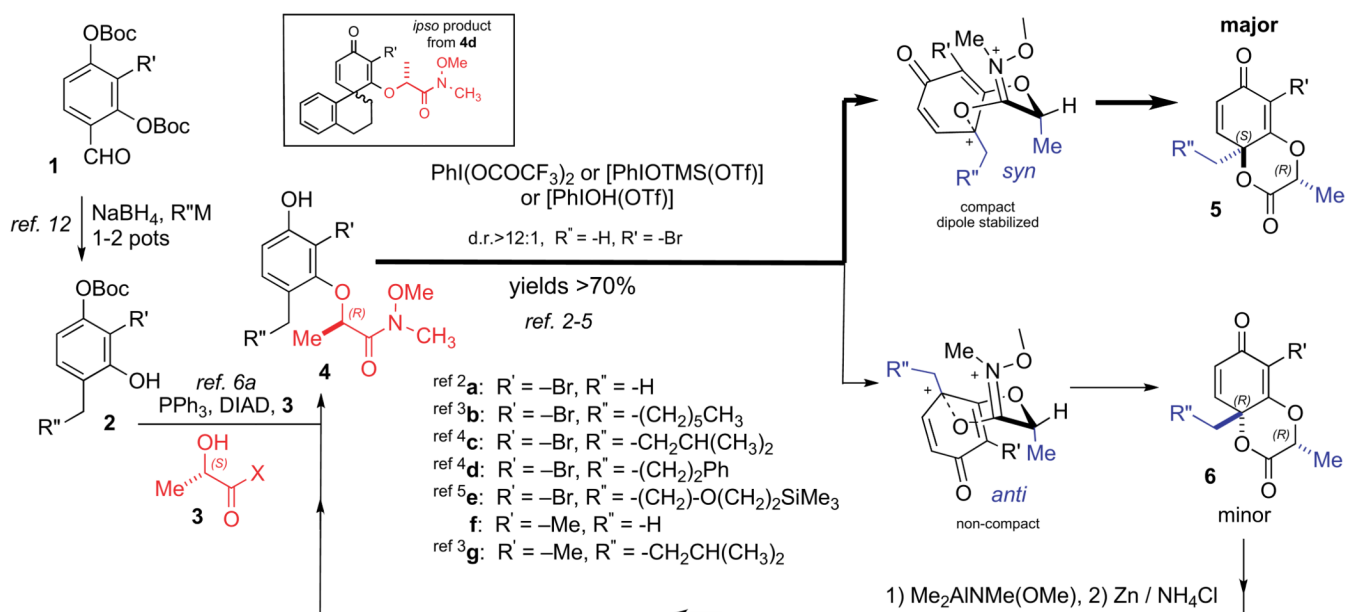
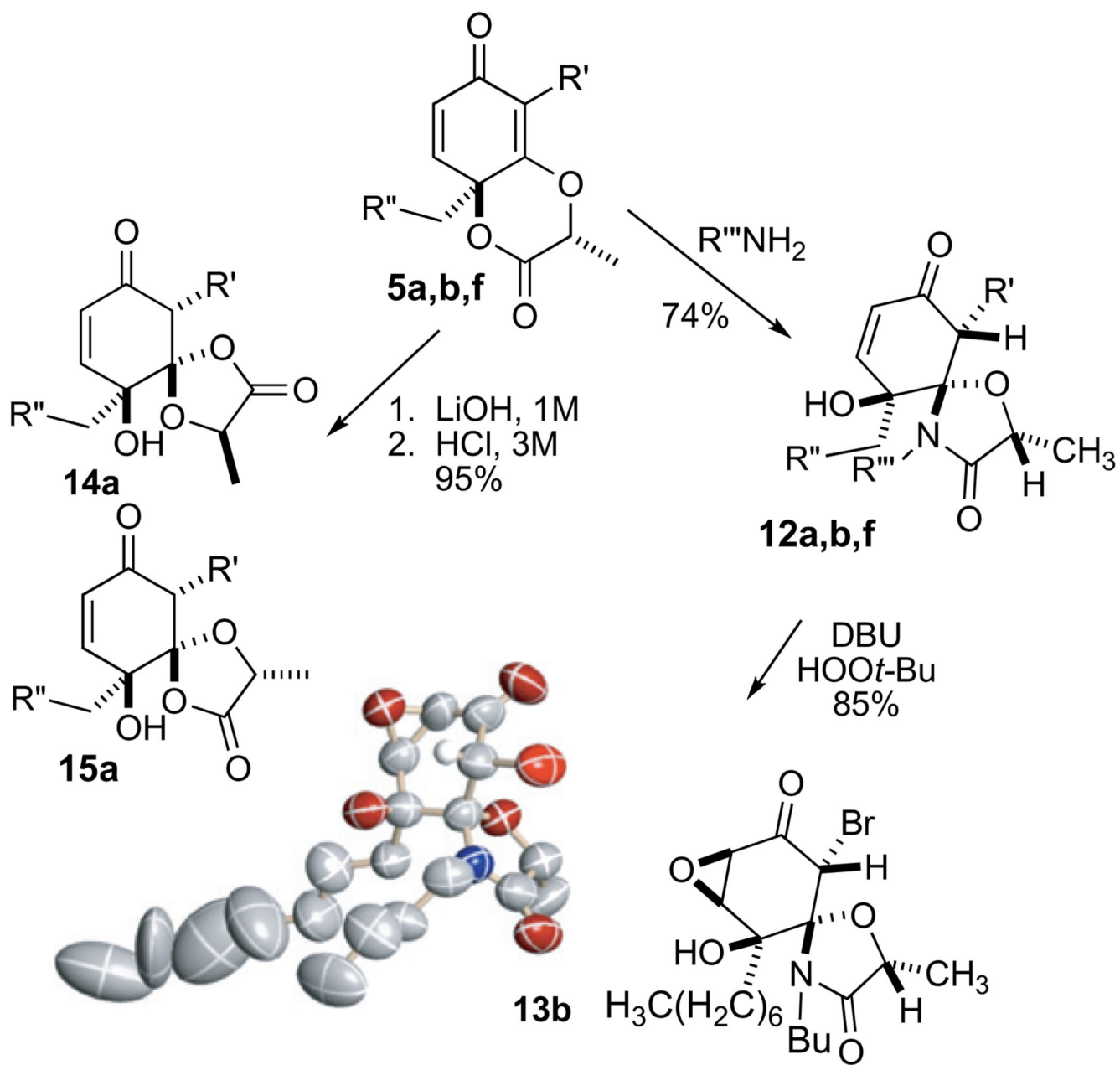**Scheme 1.**
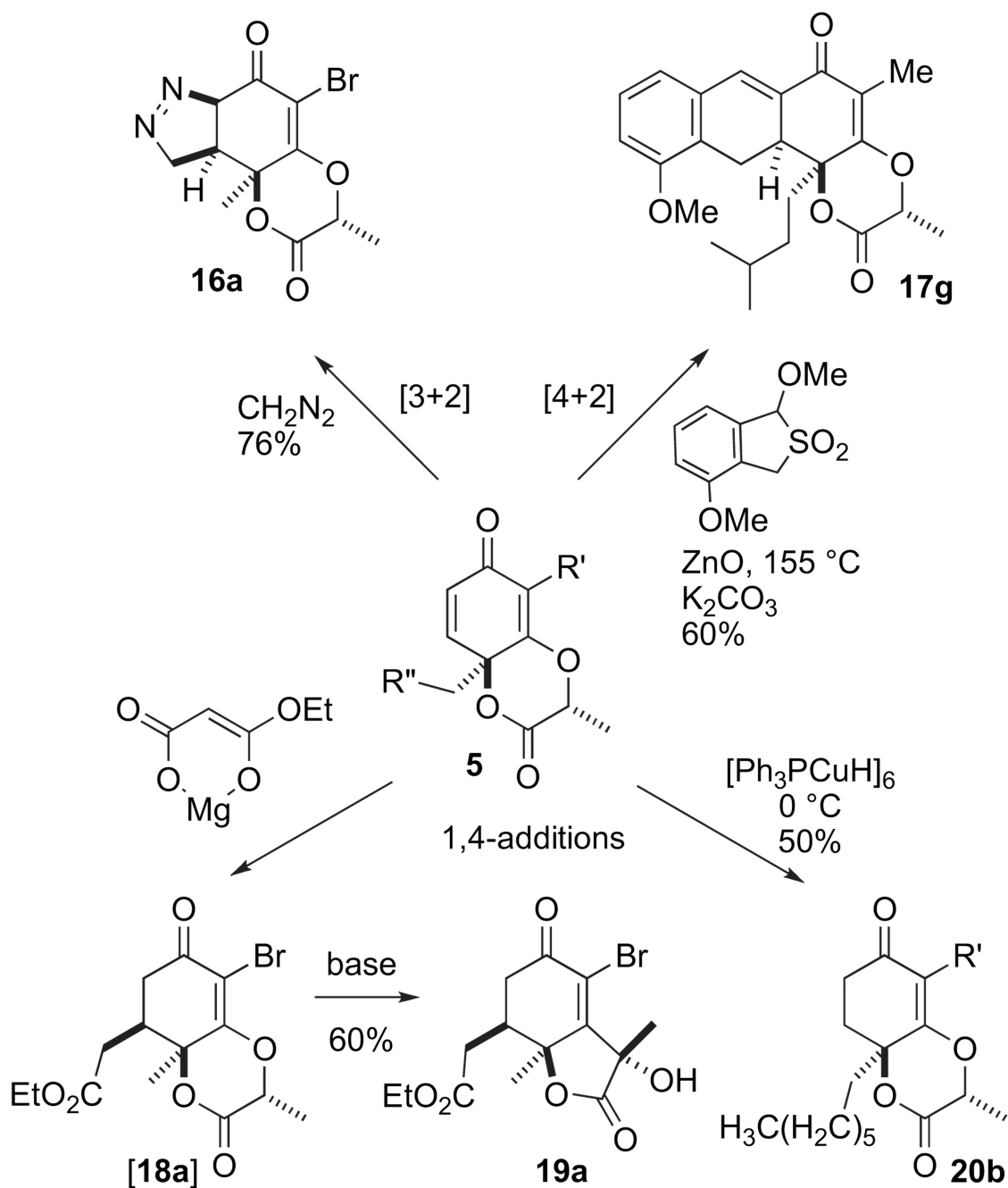Diastereoselective dearomatization of resorcinol derivatives with [PhIOTMS(OTf)].
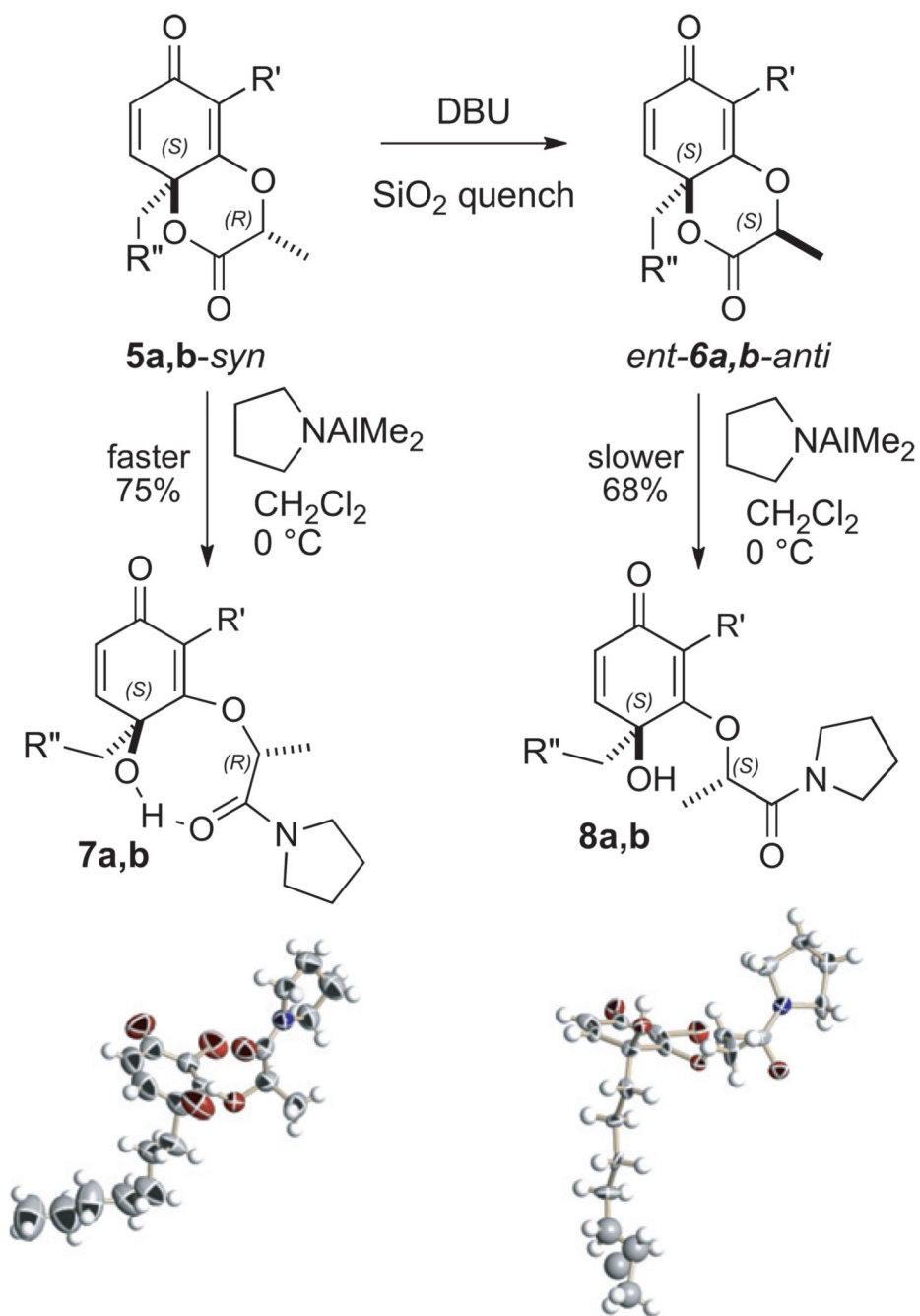
Scheme 2.
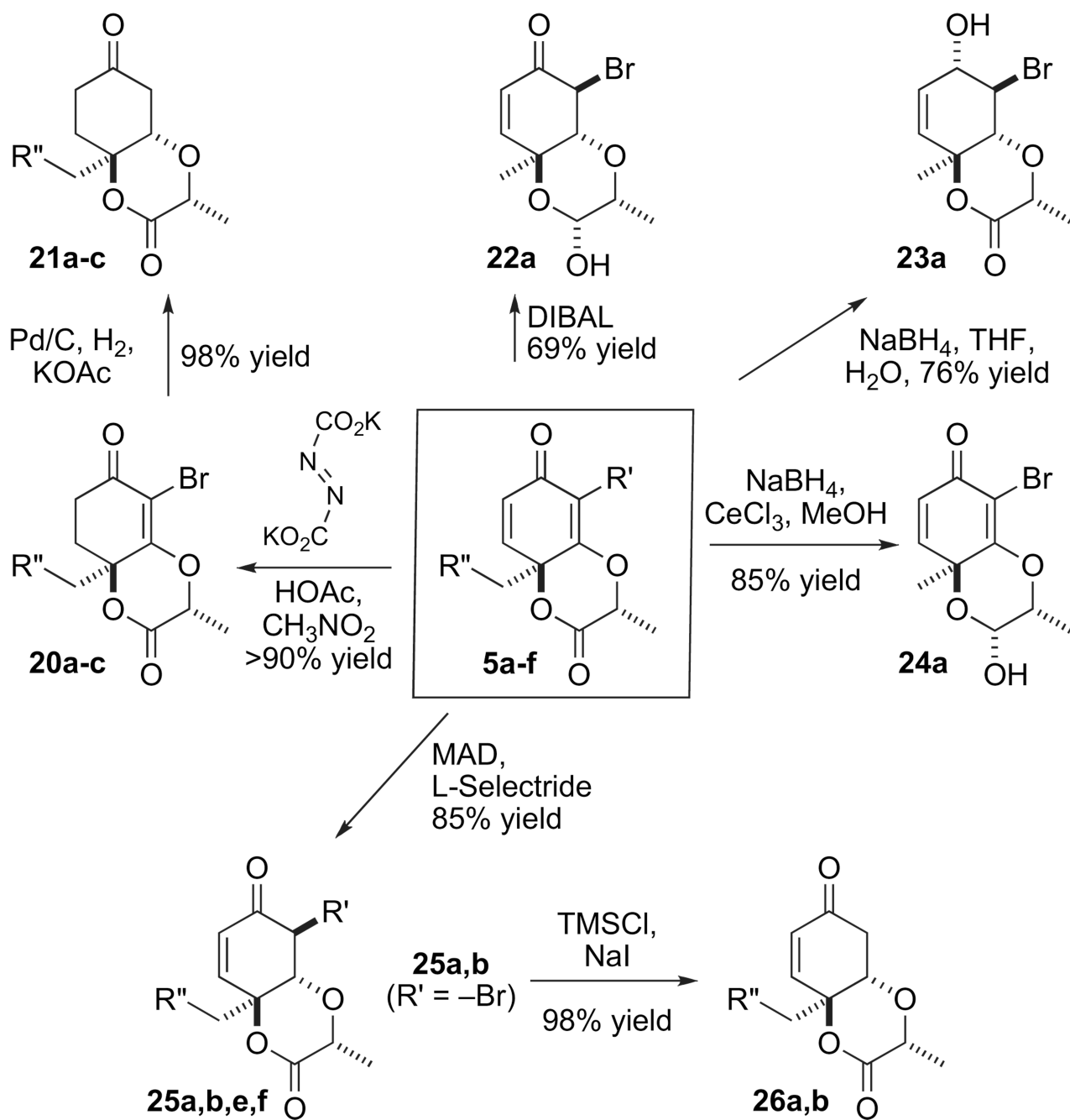Epimers displaying different reactivity.
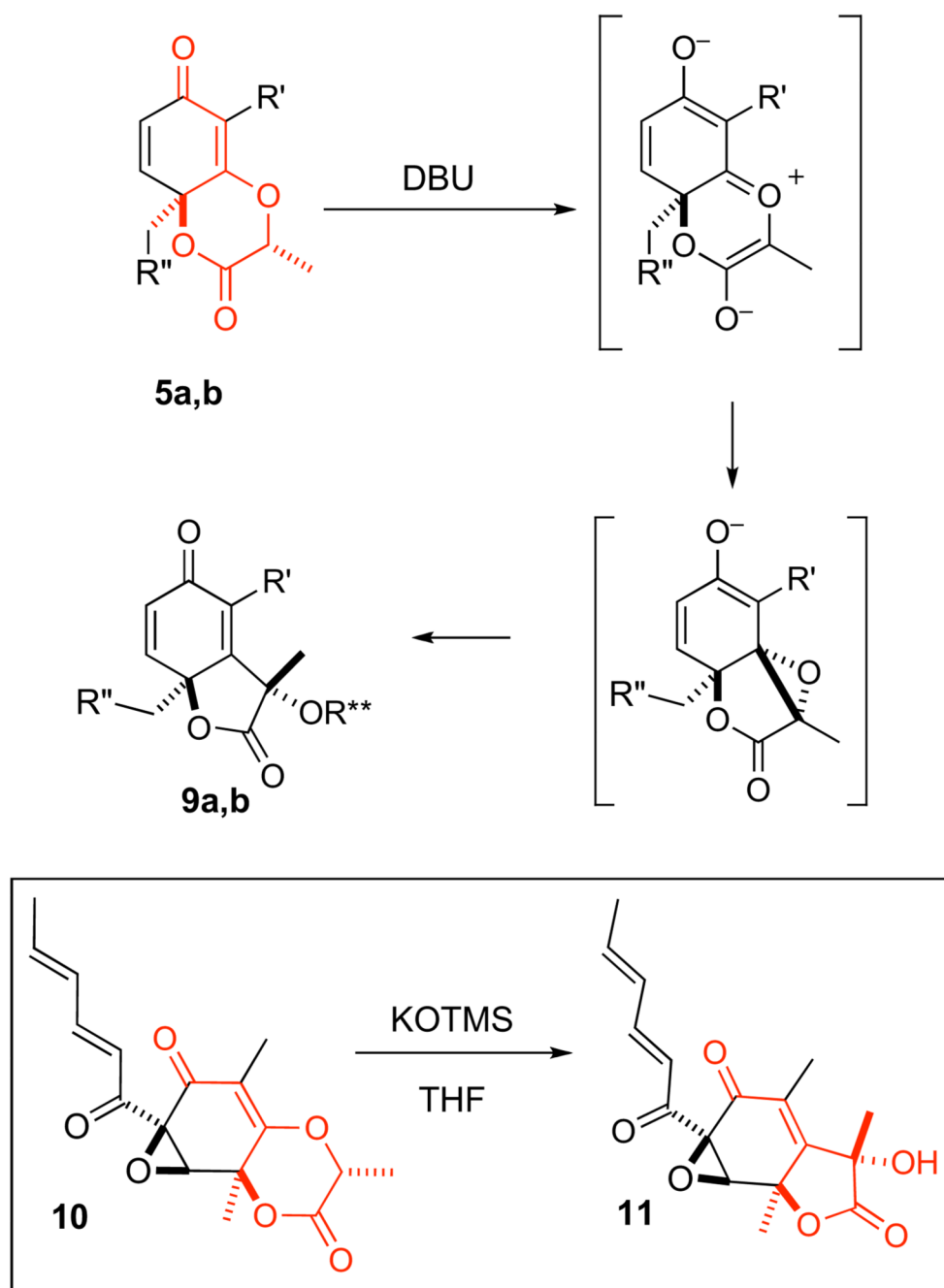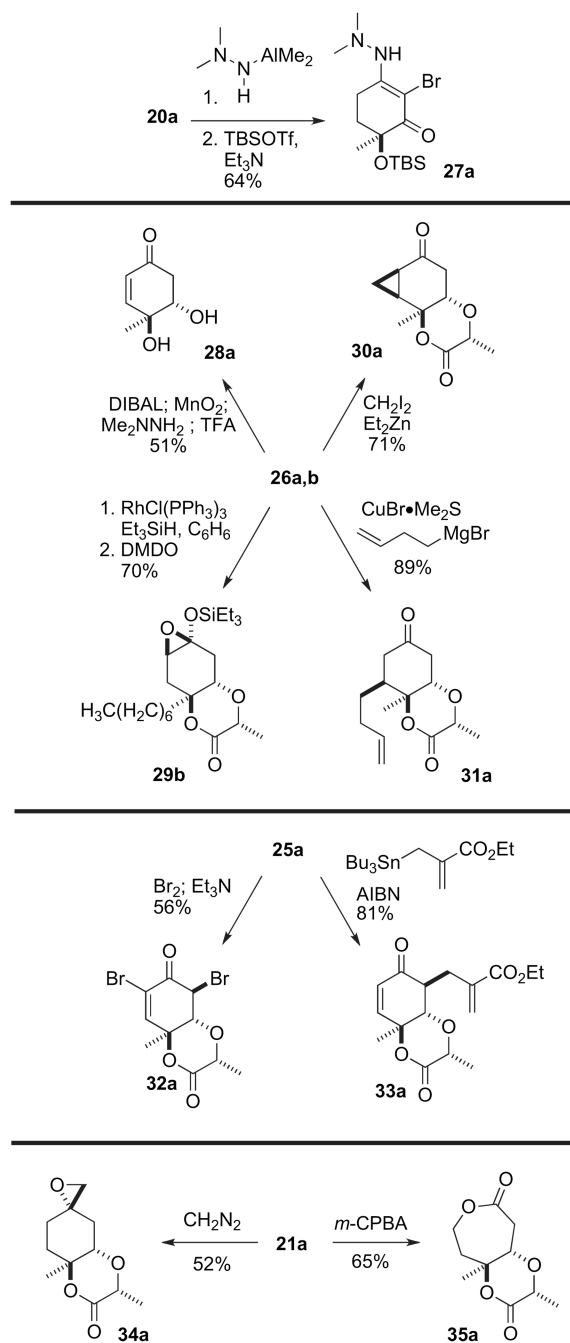
Scheme 3.
An unexpected rearrangement.

Scheme 4.
Remarkable functional group interconversions of the vinylogous ester in type **5** cyclohexadienones.

Scheme 5.
Some stereoselective [3+2] and [4+2] additions and some 1,4-conjugate additions to the enone of adduct **5**.

Scheme 6.
Unexpected reductions in rigid cyclohexadienones.

Scheme 7.
Some other useful transformations.