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Enantioselective Total Synthesis of Andrographolide and 14-Hydroxy-Colladonin: Carbonyl Reductive Coupling and *trans*-Decalin Formation *via* Hydrogen Transfer

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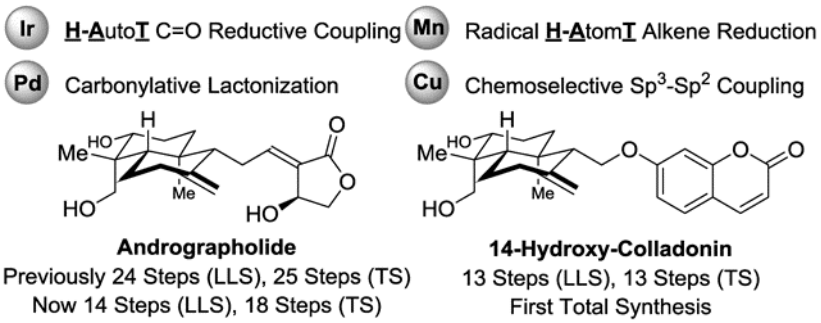
Graphical Abstract



King of Bitters. An enantioselective total synthesis of the labdane diterpenoid andrographolide, the bitter principle of the medicinal herb *Andrographis paniculata* (known as “King of Bitters”), is accomplished in 14 steps (LLS) - 10 steps shorter than the prior total synthesis. Key transformations include iridium-catalyzed carbonyl reductive coupling to form the quaternary carbon stereocenter at C4, diastereoselective alkene reduction to establish the *trans*-decalin ring, and carbonylative lactonization to install the α-alkylidene-γ-butyrolactone.

Keywords

Enantioselective; Iridium; Labdane Diterpenoid; Hydrogen Transfer

Terpenoid natural products comprise a broad and structurally diverse class of secondary metabolites with applications spanning the fields of human medicine, agrochemistry and flavor/fragrance science.[1] The challenges posed by *de novo* terpenoid construction have evoked numerous innovative synthetic methods and synthesis design concepts. The vast majority of approaches rely on polyolefin cascade cyclizations,[2,3] which often require lengthy syntheses of the requisite polycyclization precursors. As recently illustrated to great effect, convergent routes to terpene natural products have the potential to be exceptionally concise.[4] Exploiting a transfer hydrogenative coupling of primary alcohols with isoprene oxide developed in our laboratory, products of carbonyl addition bearing acyclic quaternary

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carbon stereocenters could be generated with excellent control of diastereo- and enantioselectivity (Figure 1).[5,6,7] These adducts embody a *tert*-(hydroxy)-prenyl substructure that is found in over 2000 terpenoid natural products. Using this method, convergent syntheses of the terpenoid natural products oridamycin A,[8,9] triptoquinones B and C,[10,11] and isoiresin[12,13] were accomplished in fewer steps than previously possible (Scheme 1).[14] The former 3 natural products all derive from a common intermediate, **Fragment A**, that is diversified through Suzuki cross-coupling followed by Friedel-Crafts cyclization (Scheme 1).[8]

In the course of these studies, a divergent outcome in the intramolecular Sakurai allylation[15] used to prepare Fragment **A** from compound **4** was observed (Scheme 1). Compound **4**, which is prepared in 3 steps via isoprene oxide-mediated *tert*-(hydroxy)-prenylation[5] of commercially available 5-hydroxy-2-pentanone, exists in equilibrium with it's 5-membered lactol. Using $ZnCl_2$ as the Lewis acid, intramolecular Sakurai allylation[15] occurs by way of an endocyclic oxacarbenium ion to form the [2.2.1]oxabicycle Fragment **A**. However, using BF_3•OEt_2 as the Lewis acid, Fragment **A** ring opens and eliminates to deliver the conjugated diene *iso*-Fragment **A**. Access to *iso*-Fragment **A** raised the possibility of further broadening our convergent approach to terpenoid construction by opening linear divergent routes to other terpenoid natural products through successive Diels–Alder cycloaddition-olefin reduction to generate a *trans*-decalin motif, as initially communicated in our total synthesis of isoiresin. [12,13,14] In the present article, use of this strategy as a general point of entry to diverse terpenoids is demonstrated by the enantioselective total synthesis of the labdane diterpenoid andrographolide[16–19] in 14 steps (LLS) - 10 steps shorter than the prior synthesis[19] and the first total syntheses of the coumarin-containing sesquiterpene 14-hydroxy-colladonin[20] in 13 steps (LLS), which corroborates its structural and absolute stereochemical assignment (Figure 1).

The labdane diterpenoid andrographolide is the crystalline bitter principle of the annual herbaceous plant *Andrographis paniculata* of the family *Acanthaceae*, which, among many other names, is known as "King of Bitters".[16] Native to India and Sri Lanka and used for centuries in Ayurvedic medicine, it has since entered the Chinese pharmacopeia and is now used throughout tropical regions of Asia and the West Indies. Andrographolide was first isolated in pure form in 1911,[16b] but it was not until 1963[16h] that the correct connectivity of andrographolide was proposed, and not until 1984 that it's complete stereochemical assignment was determined by single crystal X-ray diffraction.[16j] Tinctures of *Andrographis paniculata* are used in traditional medicine to treat an unusually broad range of indications and, as documented in numerous reviews,[17] literally thousands of investigations into the biological properties of andrographolide have been conducted. As reported in a 2014 quantitative proteomics screen, the myriad phenotypic effects of andrographolide may derive from its extensive adduction of proteinaceous cysteine residues.[18a] Dehydroandrographolide inhibits TMEM16A expression,[18b] which is amplified in certain cancers,[18c] demonstrating derivatives of andrographolide can have translatable effects in human cells. Remarkably, despite the enormous attention andrographolide has received, only one total synthesis has been reported.[19]

Our approach to andrographolide begins with the transfer hydrogenative *tert*-(hydroxy)-prenylation[5] of commercially available 5-hydroxy-2-pentanone **1** (Scheme 1).[14] It was found that the more Lewis acidic (*S*)-Tol-BINAP modified π-allyliridium-*C,O*-benzoate derived from 3,4-dinitro-*C,O*-benzoic acid (IrL_n, X = NO_2) performed better than our standard catalyst (IrL_n, X = CN). On 5 gram scale using low loadings of catalyst (2 mol%), the product of C–C coupling **2** could be obtained in 81% yield, 96% ee and 86:1 dr. Chemoselective allyldimethylsilylation of the primary alcohol followed by ring closing metathesis gives the cyclic allylsilane **4**,[21] which upon BF_3•OEt_2 promoted intramolecular Sakurai allylation delivers *iso*-Fragment **A**. The Diels–Alder reaction of *iso*-Fragment **A**, which creates a quaternary carbon stereocenter, posed several challenges (Scheme 2).[22] *iso*-Fragment **A** itself could not be engaged in Diels–Alder cycloaddition, due to side-reactions associated with unprotected diol. Using the *bis*-pivalate derived from *iso*-Fragment **A** (compound **5**), only highly activated dienophiles were effective partners for cycloaddition. Upon use of dimethyl acetylene dicarboxylate (DMAD), the desired cycloadduct **7** was formed as a 10:1 mixture of diastereomers. Cycloadditions of the corresponding bis-acetate and bis-isobutyrate gave 2.5:1 and 4.5:1 diastereomeric mixtures, respectively (not shown). It was posited that acetonide **6** might undergo cycloaddition with complete diastereofacial selectivity from the convex face of the bicycle. Indeed, cycloadduct **8** is formed as a single stereoisomer. Formation of the *trans*-decalin ring system of andrographolide was attempted next. Manganese-catalyzed hydrogen atom transfer (HAT) was selected for this purpose due to its ability to affect alkene hydrogenation with thermodynamically controlled diastereoselectivities, including formation of *trans*-decalins from precursors related in structure to cycloadduct **8**.[23] In the event, HAT reduction of cycloadduct **8** occurs in a completely chemoselective manner, but with exclusive formation of the undesired *cis*-decalin **9**, which was characterized by single crystal X-ray diffraction. This outcome was attributed to the conformational constraint imposed by the acetonide moiety, as HAT reduction of diol **10** delivers the *trans*-decalin **11** as a single diastereomer. The magnitude of the indicated ^{1}H NMR coupling constants between the indicated C3 methine hydrogen and the adjacent C2 methylene moieties for acetonide **8** *versus* diol **10** suggests the acetonide inverts the preferred chair-like conformer such that the C3 methine hydrogen is equatorially disposed.[24] Based on this insight, stereochemical models that account for the observed stereodivergence in the HAT reductions of compounds **8** and **10** were proposed (Scheme 2).

With this insight into the requirements for *trans*-decalin formation, the total synthesis of andrographolide was undertaken (Scheme 3). Diels–Alder cycloaddition of diene **6** with DMAD followed by hydrolysis of the acetonide *in situ* delivered cycloadduct **10** as a single diastereomer. Manganese-catalyzed HAT reduction[23] of **10** provides the *trans*-decalin **11**, which upon successive treatment with triisopropylsilyl triflate (TIPSOTf) and diisobutyl aluminum hydride (DIBAL-H) furnishes the ene-diol **12**. Reductive transposition of the less hindered allylic alcohol of **12** under Myers conditions[25] occurs in a completely chemoselective fashion to furnish homoallylic alcohol **13** as a 7:1 diastereomeric mixture at the newly formed C9 stereocenter. Using a modification of Appel's method,[26] homoallylic alcohol **13** was converted to iodide **14**, which was isolated as a single diastereomer.

Installation of the α-methylene-γ-butyrolactone was especially challenging. Diverse catalytic methods for Sp^3-Sp^2 C–C coupling of iodide **14** with vinyl bromide **15**[27] failed due to competing elimination to form diene byproducts or halide reduction. Consequently, Gillman-type C–C coupling of iodide **14** with vinyl bromide **15** was attempted.[28] To our delight, treatment of the organolithium derived from iodide **14** with 2-thienyl(cyano)copper lithium followed by exposure to vinyl bromide **15** resulted in completely chemoselective cross-coupling at the terminal vinyl bromide to provide (after hydrolysis of the acetonide *in situ*) diol **16** in 54% yield. Palladium- Xantphos-catalyzed carbonylative lactonization of bromoalcohol **16** in accordance with Buchwald's protocol delivered the α-methylene-γ-butyrolactone **17** in excellent yield,[29,30] which upon removal of the triisopropylsilyl ethers afforded andrographolide. [16–19] Whereas the prior synthesis of andrographolide required 24 steps (LLS),[19] the present route is accomplished in 14 steps (LLS).

To illustrate how the elaboration of *iso*-Fragment **A** via Diels–Alder cycloaddition-HAT reduction might serve as a general, linear divergent conduit toward other terpenoid natural products, the total synthesis of the coumarin-containing sesquiterpene 14-hydroxy-colladonin[20] was undertaken (Scheme 4). Toward this end, diol **11** was exposed to methyl chloroformate, which resulted in exclusive acylation of the less hindered primary hydroxyl group to provide the allylic carbonate **18**. Mitsunobu reaction of **18** with 7-hydroxycoumarin (also known as umbelliferone) proceeded smoothly to provide the product of substitution in 98% yield. Finally, Tsuji reduction[32] followed by fluoride-mediated removal of the silyl ethers delivered 14-hydroxy-colladonin[20] in a 13 steps (LLS). The spectroscopic characteristics of synthetic 14-hydroxy-colladonin were in excellent agreement with that of the natural material, corroborating it's structural assignment.

In summary, the enantioselective total synthesis of the labdane diterpenoid andrographolide, the bitter principle of the herbaceous plant *Andrographis paniculata* (known as "King of Bitters"), was accomplished in 14 steps (LLS) - 10 steps shorter than the prior total synthesis - and the first total synthesis of the coumarin-containing sesquiterpene 14-hydroxy-colladonin was accomplished in 13 steps (LLS). Both natural products were prepared from a common intermediate, *trans*-decalin **11**, which itself derives from the diene *iso*-Fragment **A**. Two hydrogen transfer reactions were uniquely enabling in the preparation of these compounds: the iridium-catalyzed carbonyl reductive coupling to form the quaternary carbon stereocenter at C4, and the manganese-catalyzed HAT reduction of the 1,4-cyclohexadiene **10** to form *trans*-decalin **11**. Expansion of this approach to other medicinally relevant terpenoid natural products is currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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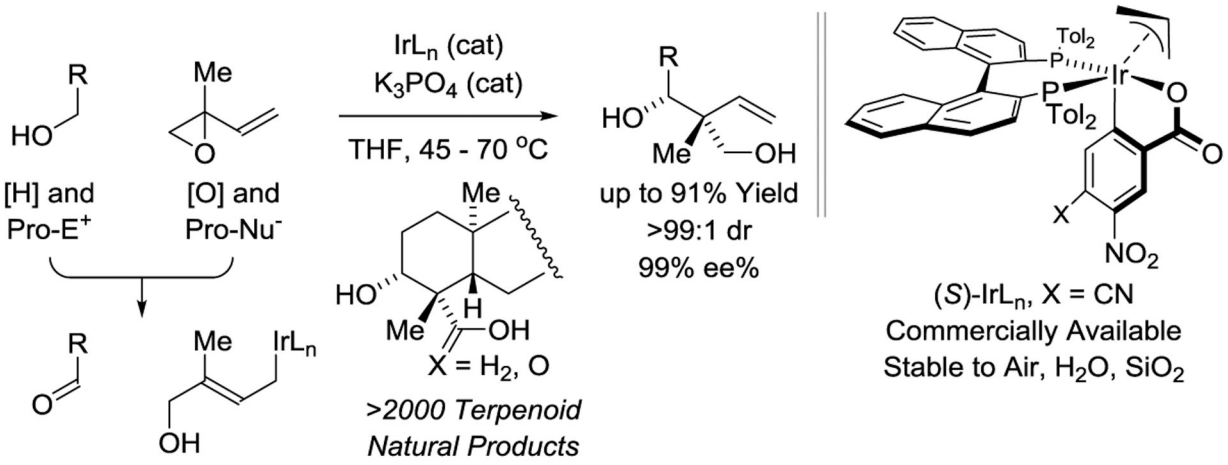
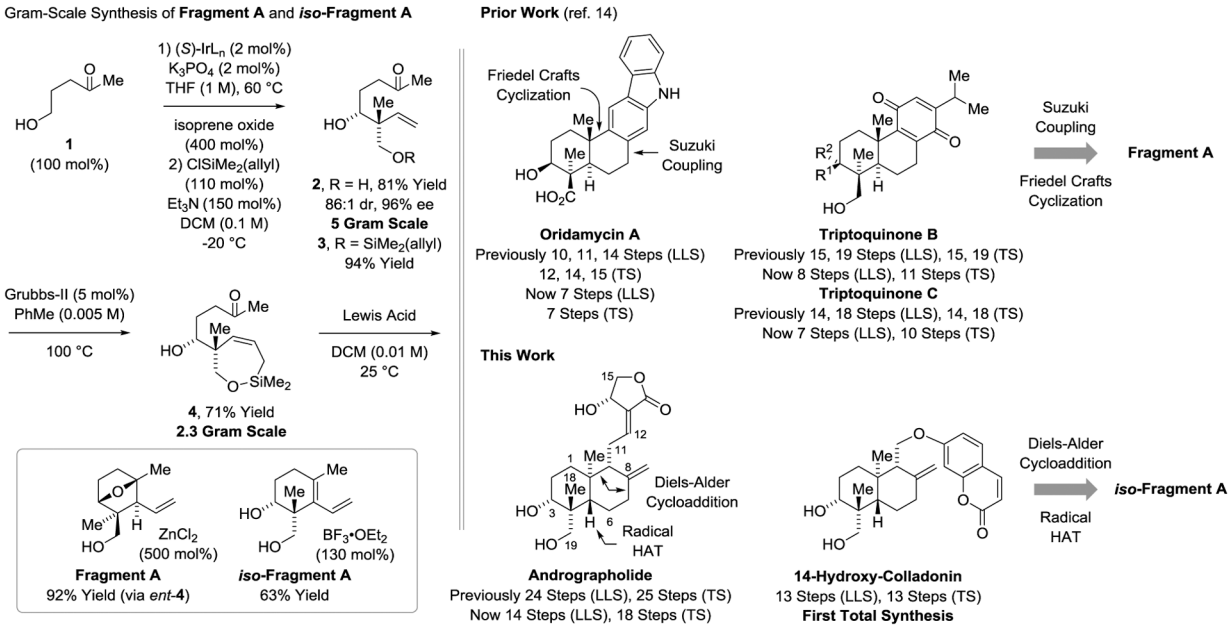


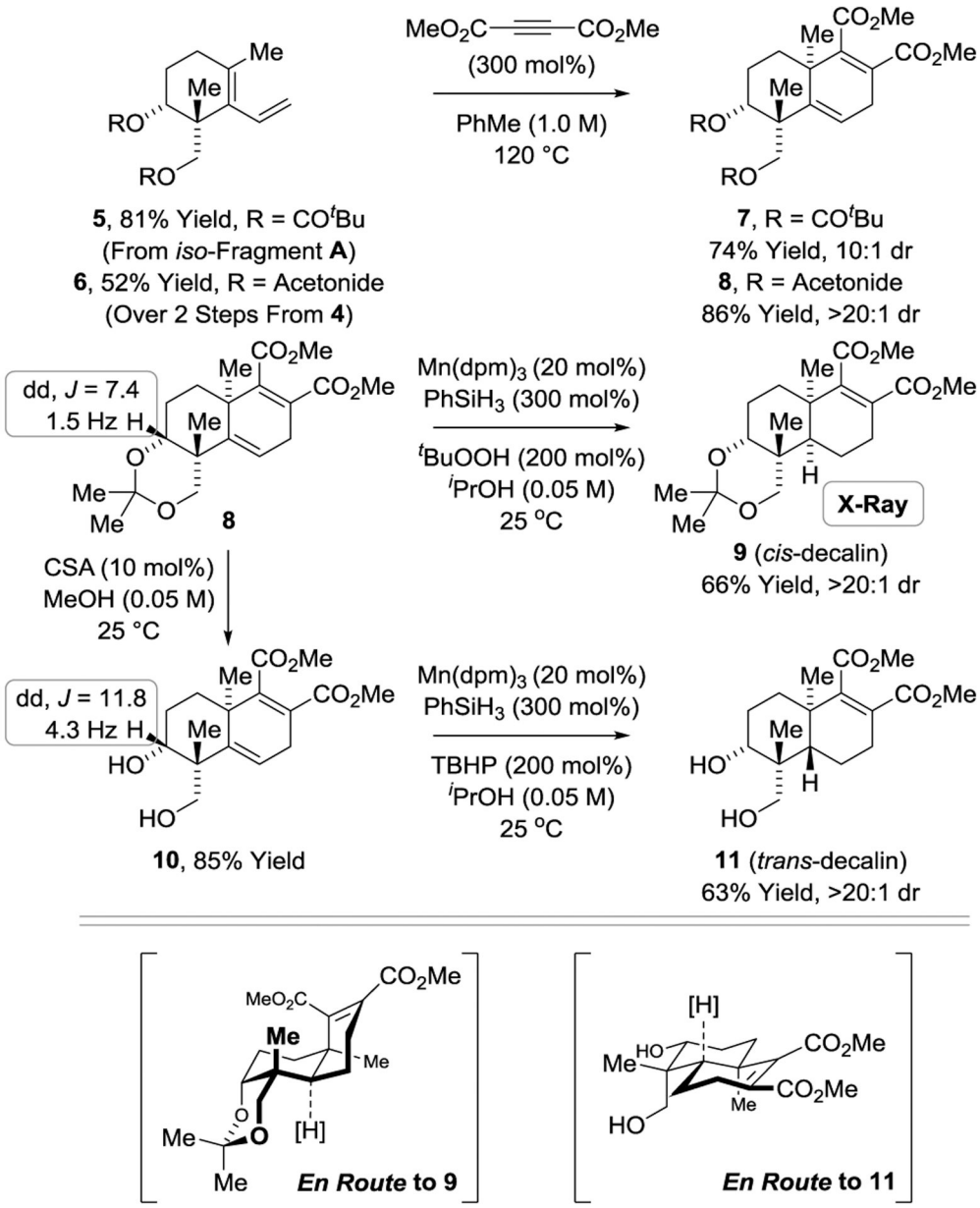
Figure 1.

Entry to terpenoid natural products via enantioselective iridium-catalyzed carbonyl reductive coupling mediated by hydrogen auto-transfer.



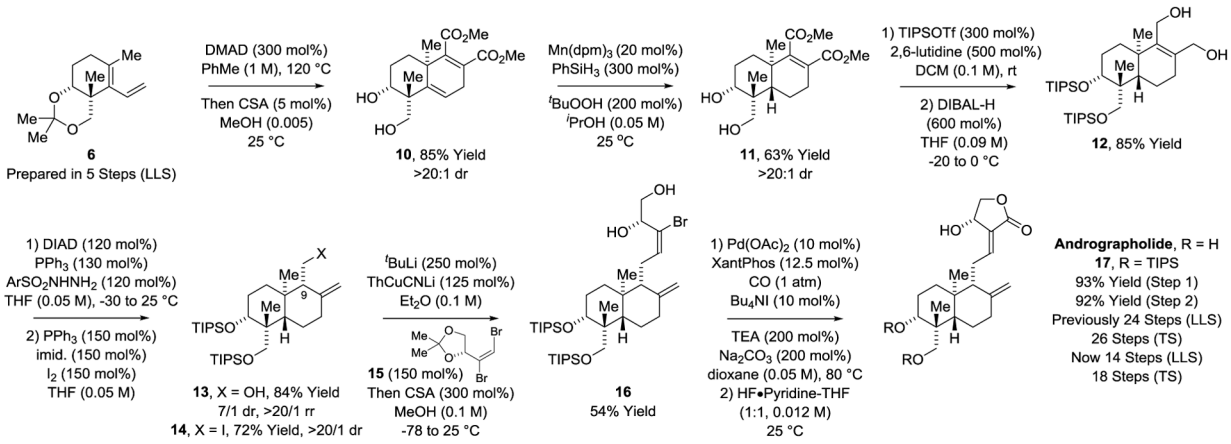
Scheme 1.

Linear divergent strategies for the total synthesis of terpenoid natural products via iridium-catalyzed carbonyl reductive coupling of 5-hydroxy-2-pentanone with isoprene oxide.



Scheme 2.

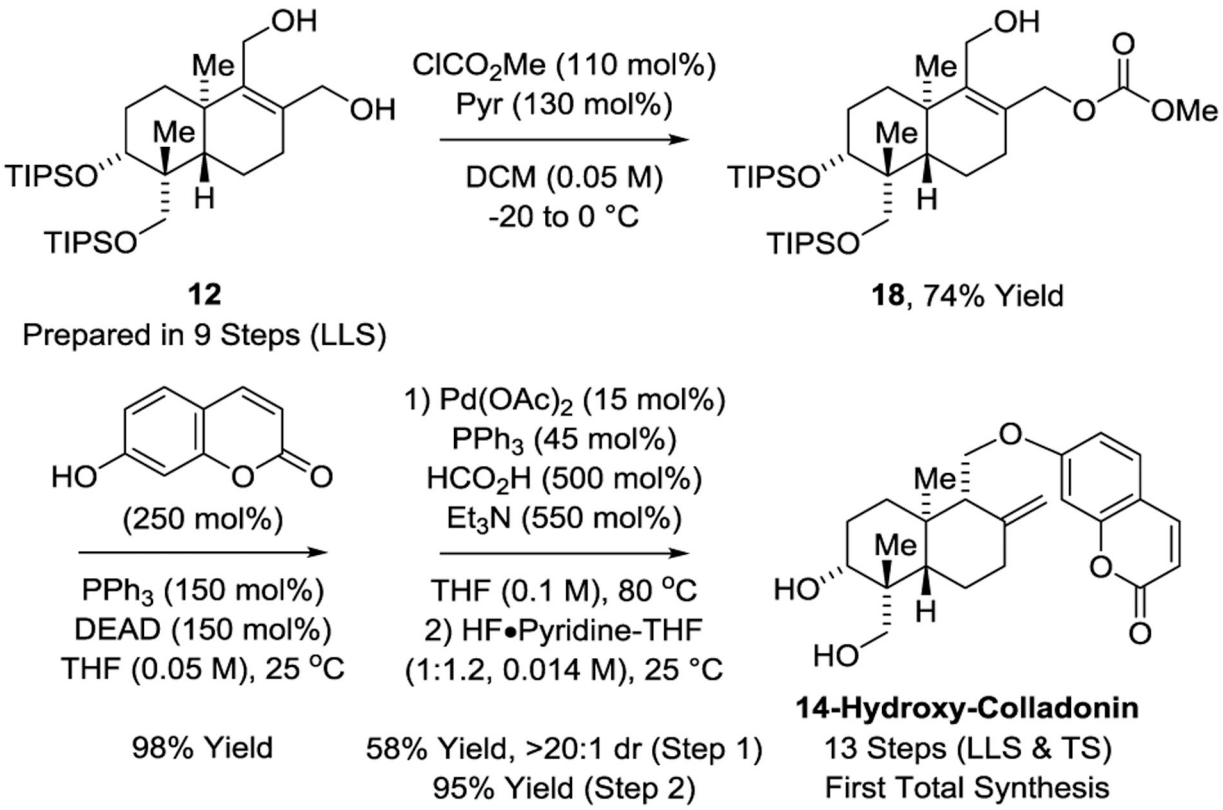
Stereodivergence in HAT reductions of Diels–Alder cycloadducts **8** and **10**.



Scheme 3.

Total synthesis of the labdane diterpenoid andrographolide.[a]

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.



Scheme 4.

Total synthesis of the coumarin-containing sesquiterpene 14-hydroxy-colladonin.

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.