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Asymmetric Total Syntheses of (−)-Variabilin and (−)-Glycinol

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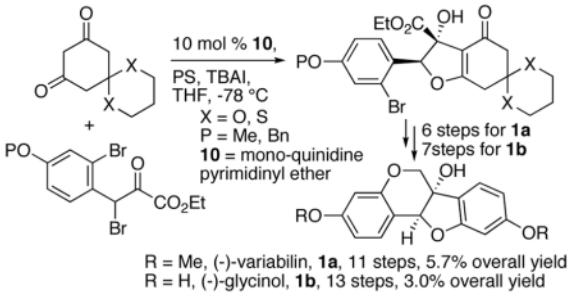
Abstract



Total syntheses of (−)-variabilin and (−)-glycinol have been accomplished, using the catalytic, asymmetric “interrupted” Feist-Bénary reaction (IFB) as the key transformation to introduce both stereogenic centers. A monoquinidine pyrimidinyl ether catalyst affords the IFB products in over 90% ee in both cases. Other key steps include an intramolecular Buchwald-Hartwig coupling and a nickel-catalyzed aryl tosylate reduction.

Variabilin (**1a**) and glycinol (**1b**) are members of the phytoalexins family produced by certain plants in response to fungal infection.[1,2] Naturally occurring variabilin occurs as the (+)- and (−)-enantiomers, both of which show antifungal activity towards *Monilinia fructicola* ($ED_{50} < 2\times10^{-5}$ M).[3] (−)-Glycinol was first isolated in 1978 by Lyne and Mulheirn from coppertreated soybean cotyledons.[4] It is believed that glycinol is the key precursor in the biosynthesis of glyceollins.[5] Burow *et al.* have recently shown that glycinol exhibits a strong in vitro estrogenic effect by binding to both estrogen receptor ERα (IC_{50} = 13.75 nM) and ERβ (IC_{50} = 9.05 nM).[6]

To date, only one asymmetric total synthesis of each target has been accomplished, both of which set the stereogenic centers by asymmetric dihydroxylation in the presence of stoichiometric amounts of OsO_4 and quinine or quinidine derivatives.[7] Here, we report total syntheses of both **1a** and **1b**, using the catalytic, asymmetric “interrupted” Feist-Benary (IFB) reaction developed by Calter *et al.* to install the chirality into the target molecules (Scheme 1).[8] Completion of the synthesis would then involve aromatization, intramolecular Buchwald-Hartwig reaction to form the benzopyranoid ring, tosylate reduction and finally deprotection in the case of glycinol. The IFB reactions would require dione nucleophiles **2a** or **2b** and the β-bromo-α-ketoester electrophiles **3a** or **3b**, which were all either known compounds or close analogues.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The synthesis of dithiane **2a** began with the addition of lithium propiolate with propylene oxide in the presence of $BF_3 \cdot Et_2O$ to afford alkynyl alcohol **4** (Scheme 2). Oxidation of **4** with the Swern reagent or the Dess-Martin periodinane provided multiple products. A successful oxidant was silica gel-supported Jones reagent (SJR), which gave a mixture of alkyne **5** and allene **6** in quantitative yield after filtration. Compound **5** was the major initial product of the reaction, but converted into **6** at −25 °C in under 12 hours. Addition of 1,3-propanedithiol to the mixture of **5** and **6** in the presence of base produced keto ester **7**, which was subjected to Dieckmann condensation to give **2a** in 47% overall yield.

Pyruvate **3a** was synthesized according to a well documented procedure beginning with the lithium trimethylethylenediamine-directed *ortho*-bromination of *p*-anisaldehyde to produce bromoaldehyde **8** (Scheme 3).[9] Submission of **8** to a Darzens reaction led to epoxide **9**, which was converted into β-bromo-α-ketoester **3a** by treatment with $MgBr_2$. [10]

With **2a** and **3a** in hand, the IFB reaction proceeded smoothly with mono-quinidine pyrimidinyl ether **10** as a catalyst and provided **11** as an inseparable 8.5:1 *E:Z* mixture of diastereomers (Scheme 4). Exposure of **11** to iodobenzene bis(trifluoromethylacetate) (PIFA) produced the corresponding, unstable dimethoxy acetal,[11] which was subjected to LiHMDS to give unstable phenol **13**. Both **12** and **13** were prone to elimination to form the corresponding furans. Tosylation of **13** afforded tosylate **14**, still as a mixture of diastereomers. However, we were able to use analytical HPLC to determine the enantio- and diastereopurity of **14**.

We were initially surprised with the (*E*)-selectivity of the IFB reaction of **2a** and **3a**, as previous examples had provided (*Z*)-selectivity, but further analysis of factors governing the diastereoselectivity of the IFB reaction provided a rationale (Figure 2). In general, the IFB reaction of substituted bromoketoesters proceeds via a dynamic, kinetic resolution, with tetrabutylammonium iodide (TBAI) serving to convert the bromide into the corresponding iodide and then constantly racemize this compound. The previous examples using unsubstituted aryl substituents yielded the (*Z*)-*R,R*-product, with both the catalyst and the substrate favoring attack, via a transition state favored by the Felkin-Nguyen model with a strongly electron-withdrawing substituent, on the *Re*-face of the (*S*)-enantiomer of the haloketeoester.

However, the *ortho*-substituent in the current substrate sterically disfavors this mode of attack, so the substrate-catalyst combination now favors *Re*-face attack on the *R*-enantiomer, leading to the (*E*)-*R,S*-stereoisomer. The *ortho*-bromine cannot rotate away from this interaction, as to do so would place the bromine in an electronically unfavorable interaction with the carbonyl oxygen or the iodine.

Continuing with the synthesis, the reduction of **14** first provided the aldehyde, which was then immediately resubmitted to a second reduction to afford 1,2-diol **15** (Scheme 5). Exposure of **15** to modified Buchwald-Hartwig coupling conditions gave dihydrobenzopyran **18**, which we were able to isolate in high diastereo-purity.[12] Initial attempts to reduce **18** using the conditions of Lipshutz and Kogan afforded **1a**, but with irreproducible conversions.[13] After experimenting with different hydride and nickel sources, we found that use of the THF-soluble $LiBH_4$ and the formation of nickel(0) from *in situ* reduction of $NiCl_2$ reliably afforded variabilin **1a**. The analytical data for the product matched those reported previously for (−)-variabilin.[7a] In total, this synthesis required 11 steps with 5.7% overall yield. The bis-demethylation of variabilin **1a** into glycinol **1b** afforded the furan under Lewis acidic conditions, and gave low and irreproducible conversion under nucleophilic conditions. Therefore, we developed an alternative synthesis of glycinol that employed more easily removable protecting groups from the beginning.

This synthesis of glycinol began with the construction of 1,3-dioxane **2b**. Treatment of acetonedicarboxylic acid **19** with $TMSO(CH_2)_3OTMS$ in the presence of a catalytic amount of TMSOTf yielded **20**.[14] Exposure of **20** to MeMgBr in CH_2Cl_2 at −78 °C for 12 h afforded keto ester **21** in moderate conversion, but we were able to recover the unreacted starting material. Dieckmann condensation of **21** promoted by LDA provided **2b** in a similar fashion to the cyclization of **7** to **2a**.

We prepared β-bromo-α-ketoester **3b** through known bromoaldehyde **22** (Scheme 7). [15] Addition of N,N′-dimethylethylenediamine to 4-hydroxylbenzaldehyde in refluxing toluene afforded the aminal. *ortho*-Metallation, bromination and hydrolysis provided aldehyde **22**, which was benzylated to give **23**. Submission of **23** to Darzens reaction and subsequent ring-opening afforded **3b**.

The IFB reaction of **2b** and **3b** proceeded smoothly with **10** as the catalyst and provided **25** in a 10:1 *E:Z* ratio (Scheme 8). In this series chromatography allowed us to remove most of the (*Z*)-diastereomer. Aromatization of **25** with *t*BuOK followed by tosylation afforded tosylate **27**. We were able to use analytical HPLC to determine the enantio- and diasteropurity of this compound.

Two-stage reduction of **27** with $LiBH_4$ gave diol **28**, which was subjected to our modified Buchwald-Hartwig conditions to give dihydropyran **29** (Scheme 9). Reduction of the aryl tosylate afforded alcohol **30**. We accomplished removal of the propylene glycol group from **30** by oxidation with DMP followed by elimination with NEt_3. Finally, deprotection of the aryl benzyl group by transfer hydrogenation provided (−)-glycinol **1b** in 90% yield. The analytical data for this product matched those reported previously for (−)-glycinol.[4,7b] This synthesis required 13 steps with 3.0% overall yield.

In conclusion, we have accomplished the catalytic, asymmetric total syntheses of (−)-variabilin and (−)- glycinol by employing the “interrupted” Feist-Benary reaction as the key step to introduce both stereogenic centers simultaneously. Both syntheses proceed in high enantio- and diastereoselectivity. The methodology developed should be applicable to the syntheses of other natural products with dihydrobenzofuran moieties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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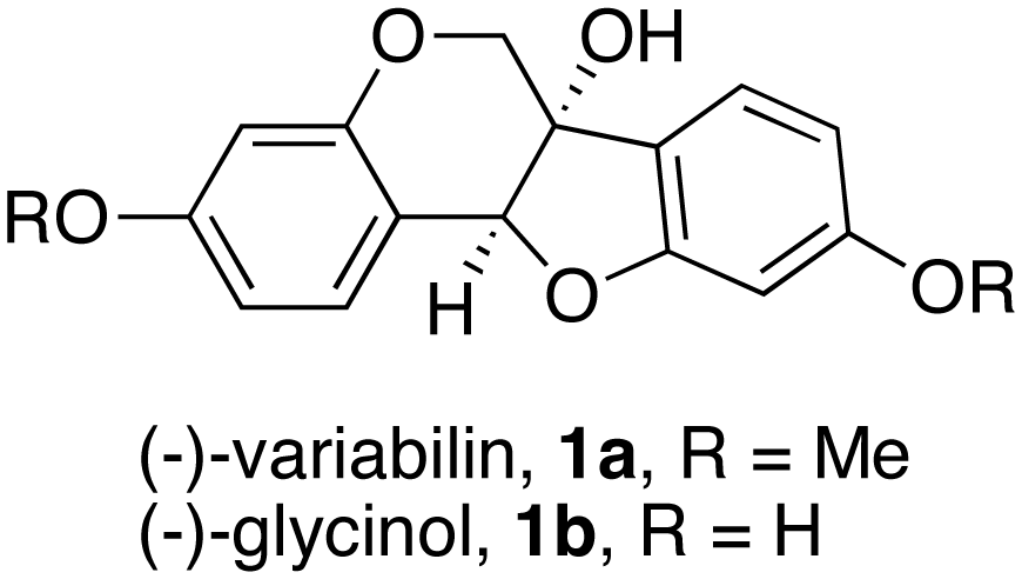


Figure 1.
Structures of Variabilin (**1a**) and Glycinol (**1b**)

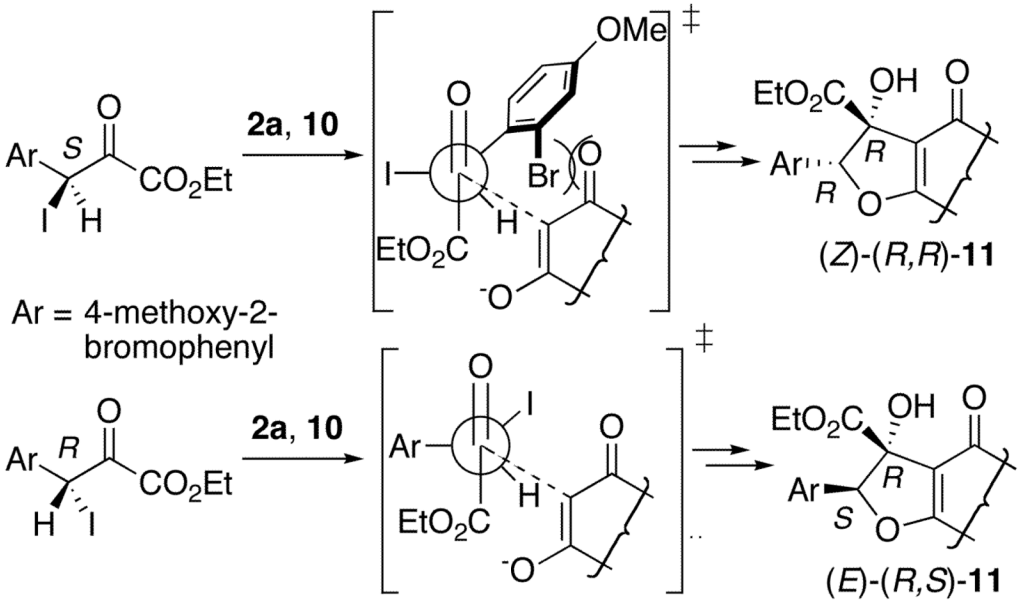
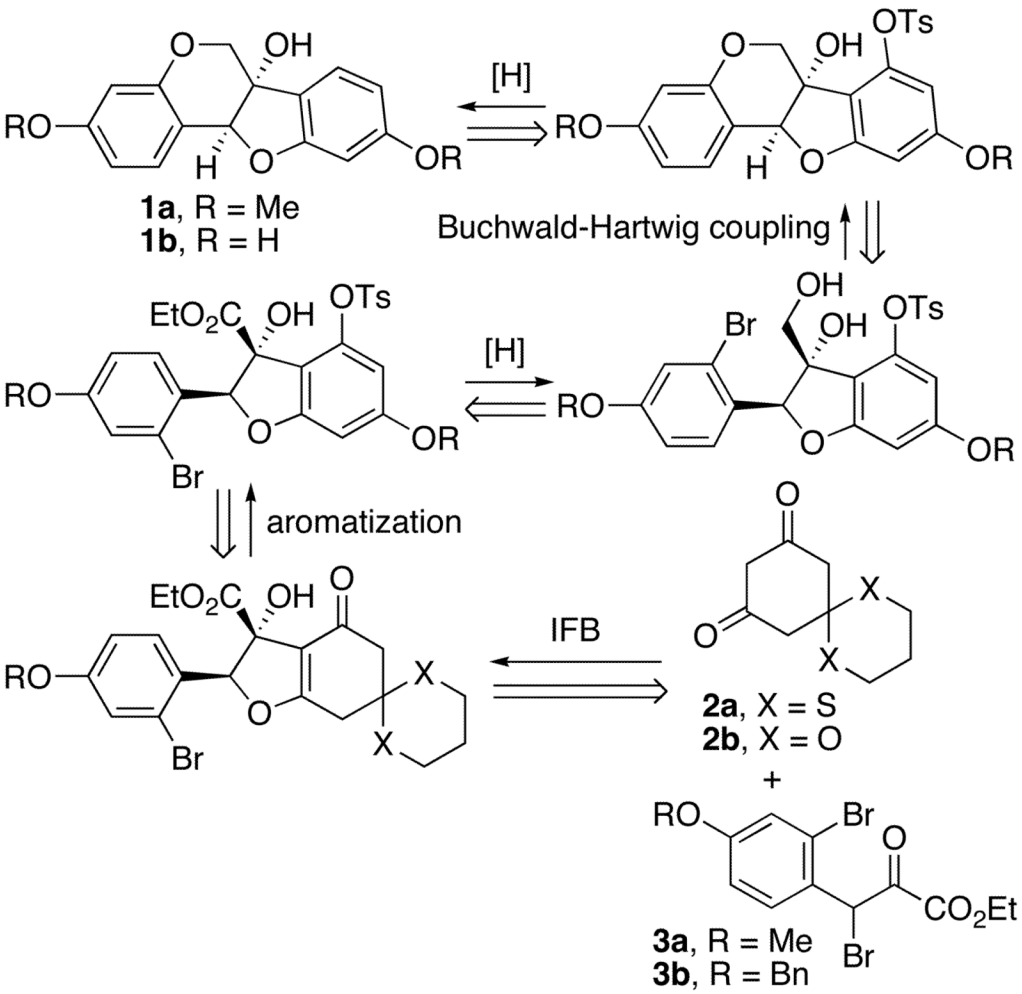
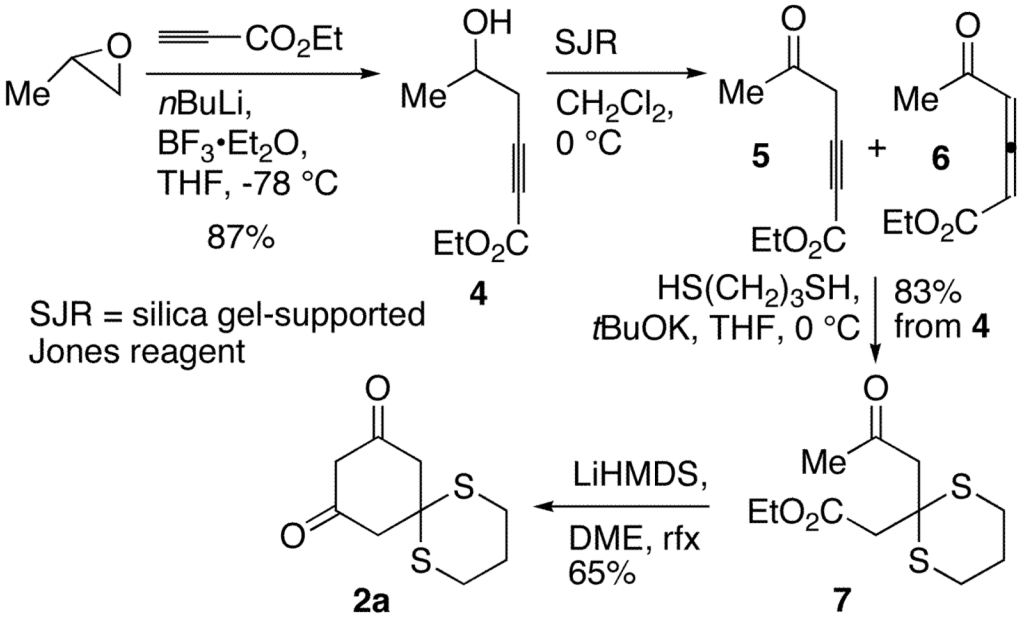


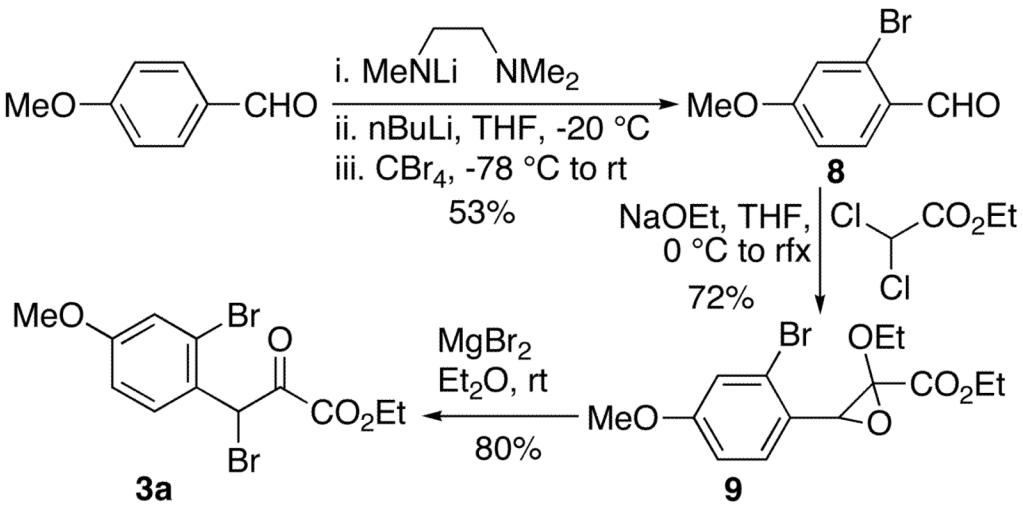
Figure 2.
Transition-state models for the IFB reaction. Catalyst omitted for clarity.



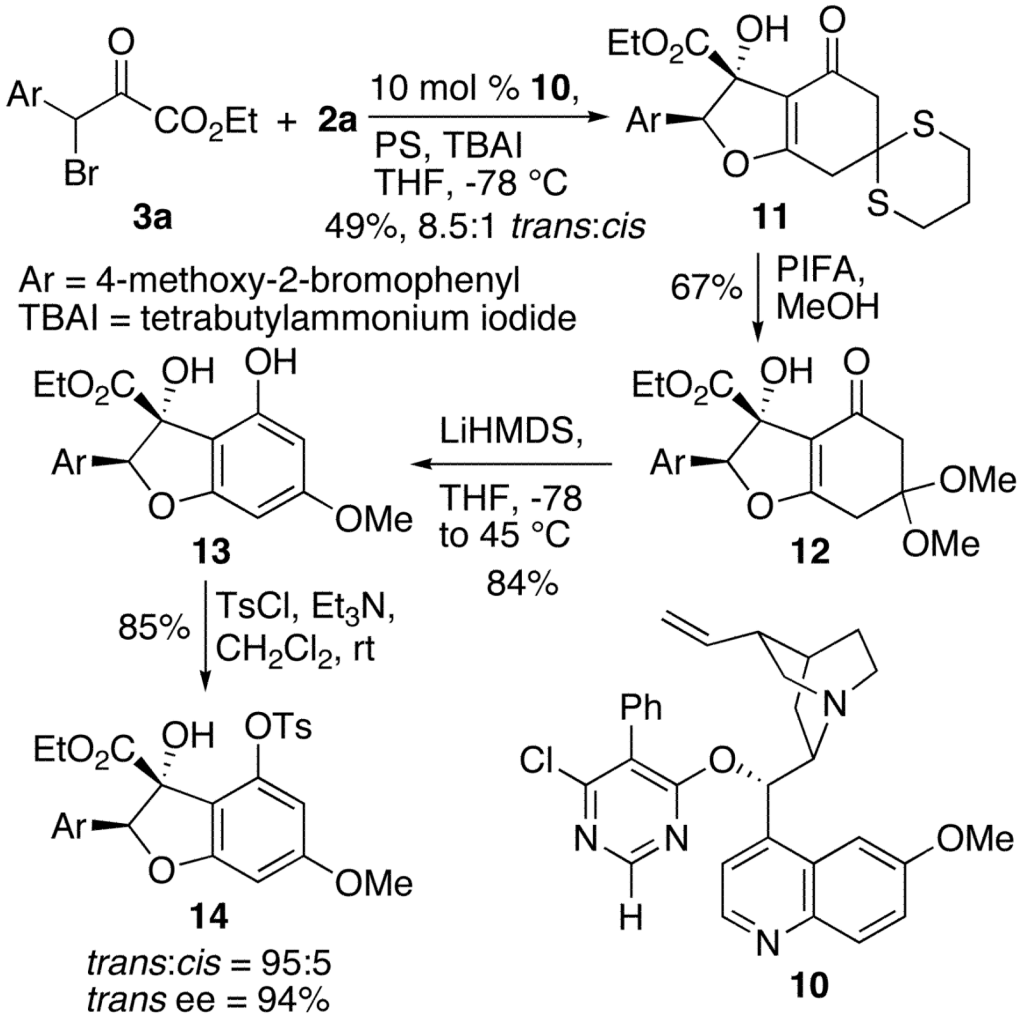
Scheme 1.
Retrosynthetic Plan for **1a** and **1b**



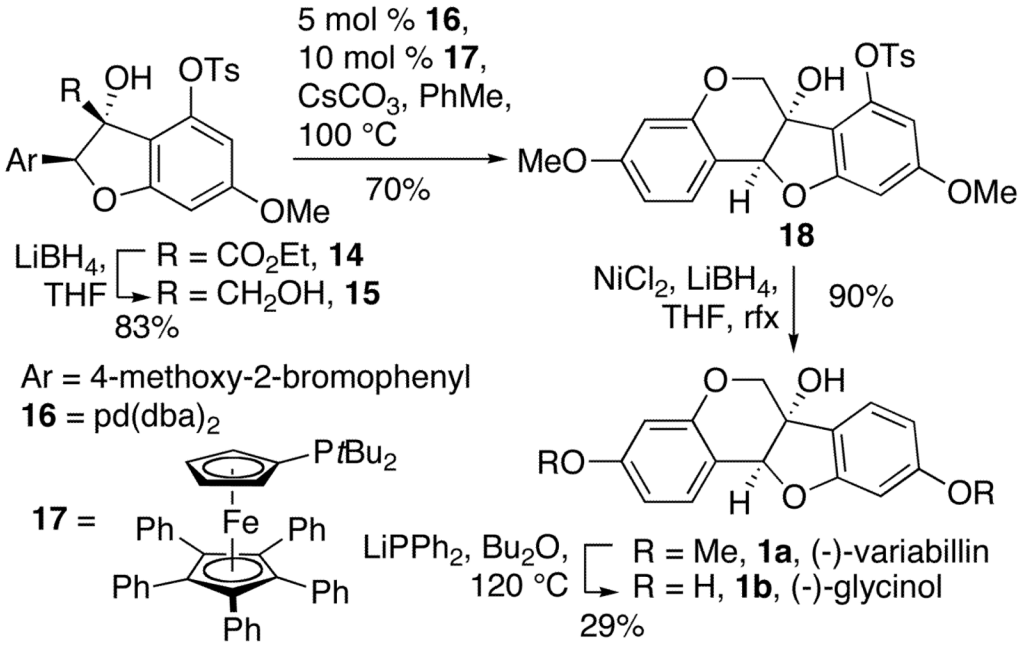
Scheme 2.
Synthesis of Dithiane **2a**



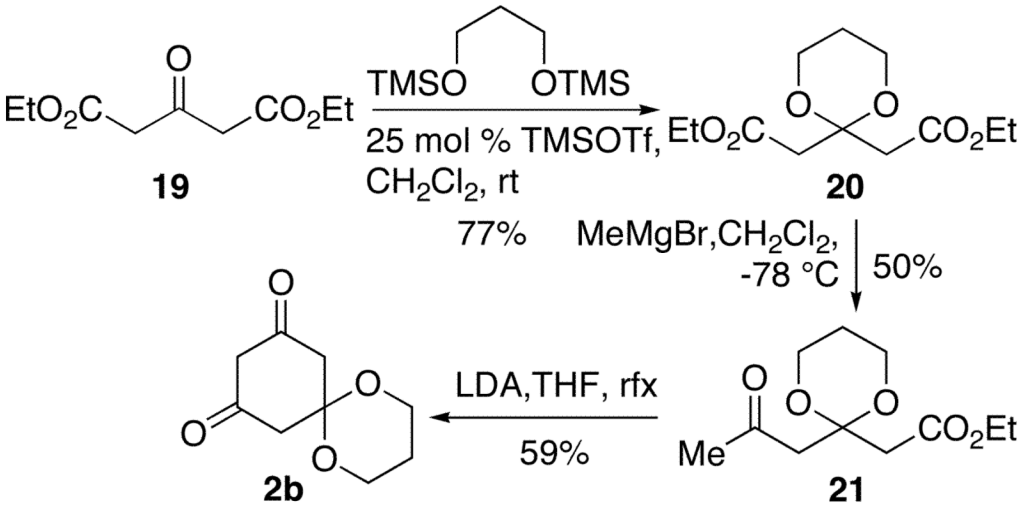
Scheme 3.
Synthesis of Pyruvate **3a**



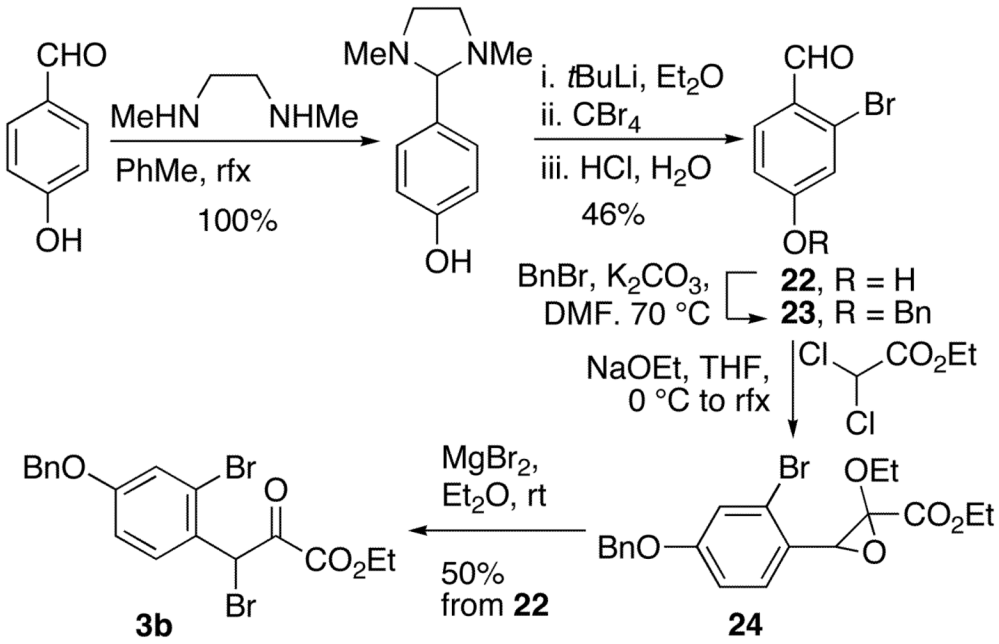
Scheme 4.
Synthesis of Tosylate **14**



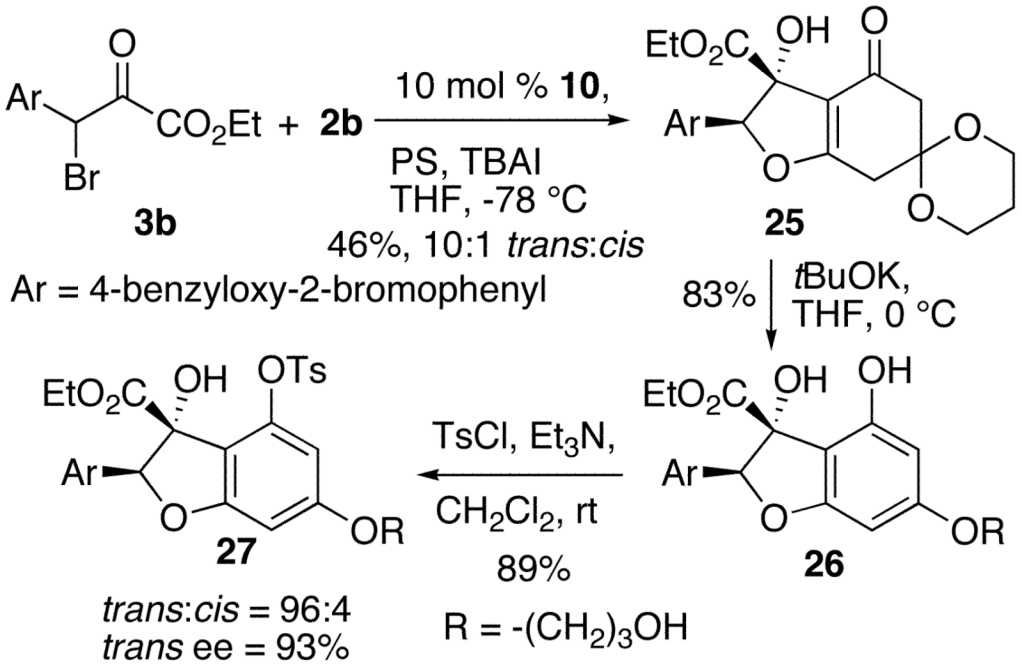
Scheme 5.
Synthesis of Variabilin **1a**



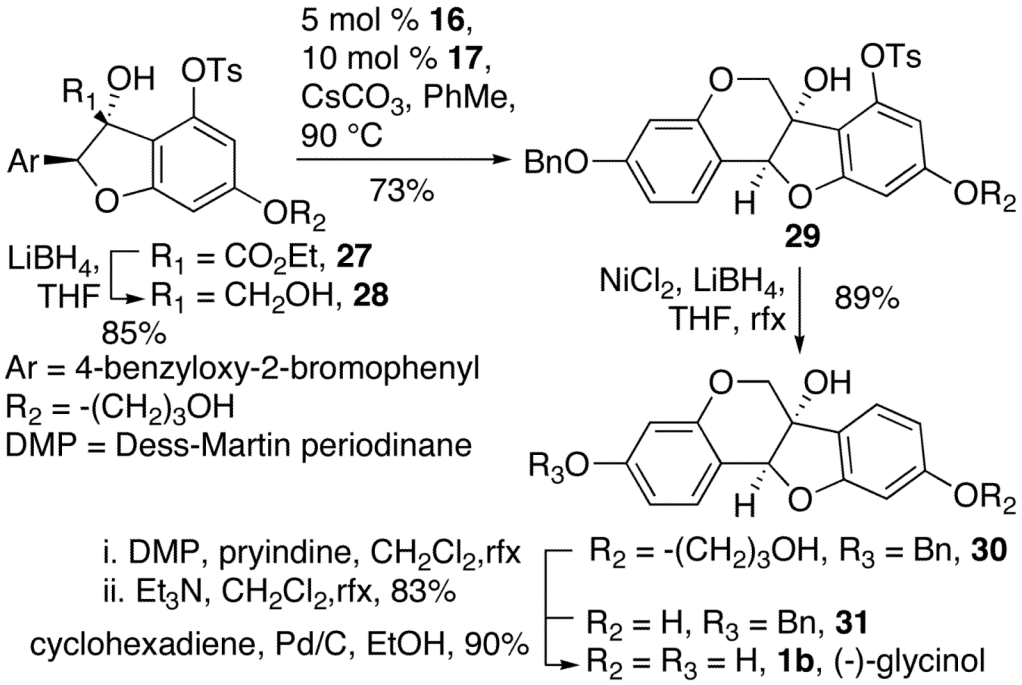
Scheme 6.
Synthesis of Dioxane **2b**



Scheme 7.
Synthesis of Bromoketone **3b**



Scheme 8.
Synthesis of Tosylate **27**



Scheme 9.
Synthesis of Glycinol **1b**