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Traceless Stereoinduction for the Enantiopure Synthesis of Substituted-2-Cyclopentenones

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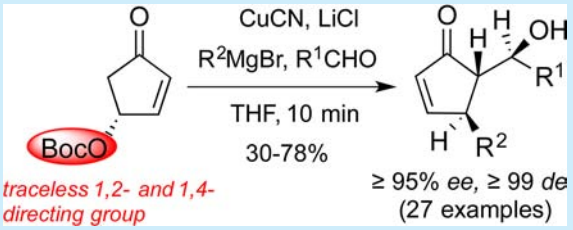
Supporting Information

ABSTRACT: The pseudoenantiomeric 4-O-Boc- and 4-OPMP-cyclopent-2-enones, readily available from hydroxymethylenefurane on multigram scale, are demonstrated to be exceptional building blocks for the synthesis of enantiopure 4-alkyl-5-(1′-hydroxyalkyl) substituted 2-cyclopentenones and derivatives thereof. The 4-OR substituent acts as a traceless stereoinducing element, conferring not only 1,2- but also 1,4-stereocontrol with excellent selectivity. The methodology developed here was applied for the rapid synthesis of natural products and biologically active 2-cyclopentenones such as TEI-9826, guaianes, and pseudoguaianolides.



Chiral 4-alkyl-5-(1-hydroxyalkyl) substituted-2-cyclopentenones **1** and derivatives thereof are important constituents of numerous natural products and biologically active drugs.[1] For example, prostaglandin analogues **2**[2] and **3**[3] have strong antitumor activity, and especially the latter was shown to retain *in vivo* activity against *cis*-platin-resistant tumors (Figure 1). Sesquiterpenoid **4**[4a] was found to be a submicromolar

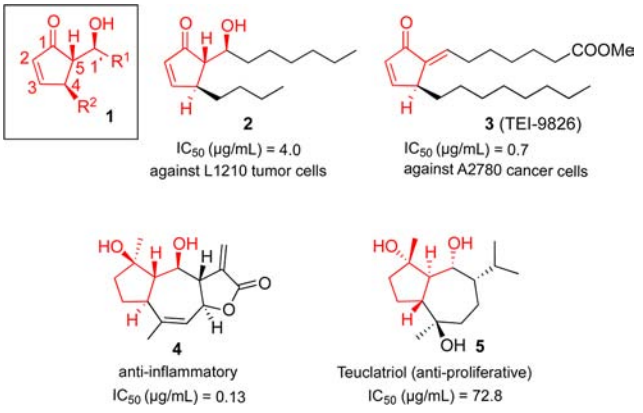
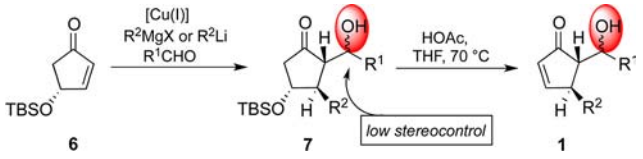


Figure 1. Bioactive substituted 2-cyclopentenones, pseudoguaianolide, and guaiane molecules.

inhibitor against LPS-induced nitric oxide production in RAW264.7 macrophages, while teuclatriol **5** shows strong antiproliferative effects on human activated peripheral blood lymphocytes.[4b,c]

With the pioneering work of Noyori et al.[5] utilizing 4-siloxy-2-cyclopentenone **6** as a key building block for the synthesis of prostaglandins (Scheme 1), a reliable strategy toward enantiopure cyclopentenones was established, being broadly applied by many.[6] Conjugate *anti*-addition of nucleophiles to **6** in the 3-position controlled by the adjacent siloxy group

Scheme 1. Synthesis of Chiral Cyclopentenones According to Noyori et al.



followed by an aldol reaction in the 2-position *anti* to the nucleophile just introduced was developed. Subsequently, the siloxy group can be eliminated to generate substituted 2-cyclopentenones. With the advent of asymmetric conjugate additions, it was demonstrated that 2-cyclopentenone can be used directly as a starting material for the synthesis of enantiopure cyclopentanones.[7a] Other strategies toward the target structure have been reported as well;[7b] however, mixtures of epimers at C-1′, often in ratios close to 1:1, are generally obtained with only a few exceptions that require sterically demanding aldehydes.[6d,7c]

We report here the pseudoenantiomeric building blocks (*R*)-**10** and (*S*)-**11**[8] (Scheme 2) as exceptional starting materials for the one-flask synthesis of the target structure **1** with excellent enantio- and diastereocontrol including the C-1′ position. The 4-oxo-substituents in (*R*)-**10** and (*S*)-**11** act as traceless stereoinducing elements that relay not only 1,2- but also remote 1,4-stereocontrol in a cascade of nucleophile addition/aldol reaction/elimination (Table 1, Scheme 3). Moreover, it is demonstrated that racemic α-chiral aldehydes are resolved under the reaction conditions, allowing the one-step construction of cyclopentenones with 4-contiguous stereocenters (Scheme 5b).

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Scheme 2. Multigram Synthesis of the Pseudoenantiomeric Building Blocks (*R*)-11 and (*S*)-11

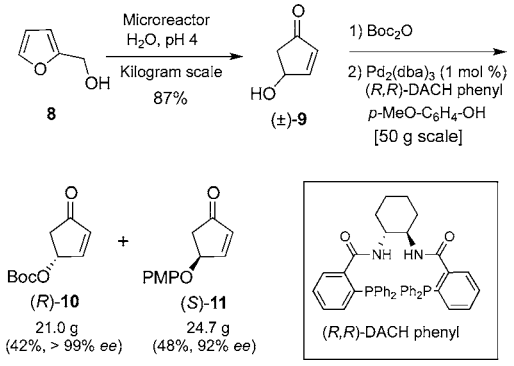
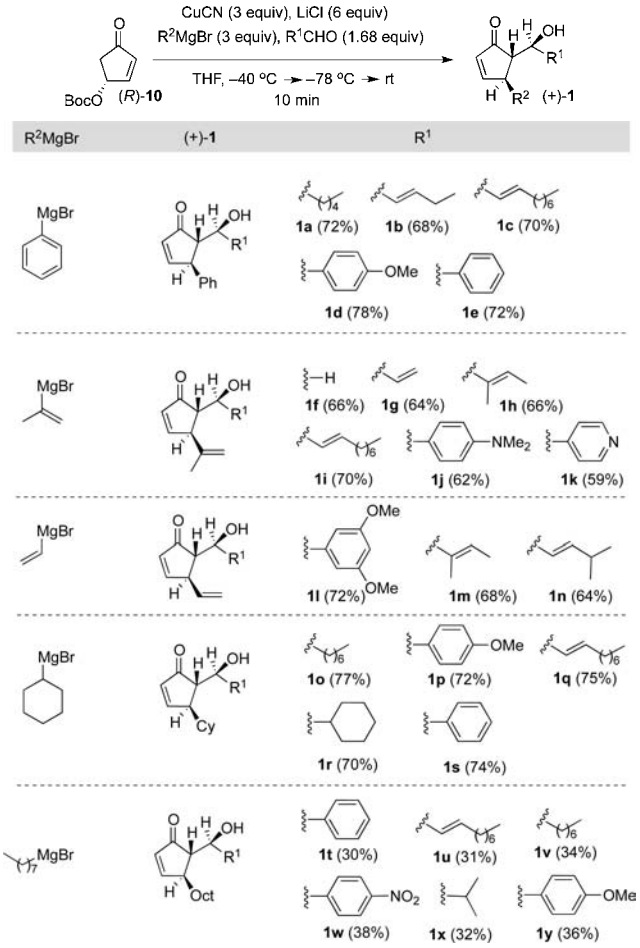


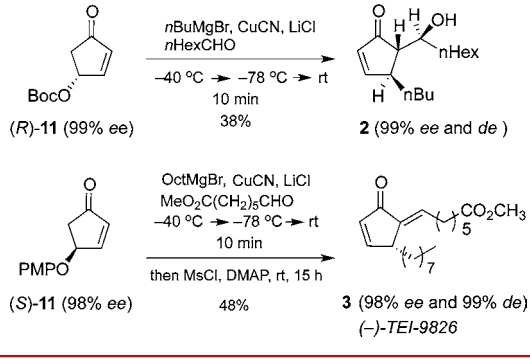
Table 1. Synthesis of Enantiopure Cyclopentenones (+)-1[a]



[a]All products were obtained with ≥99% *de* (^{1}H NMR of the crude products). **1a**–**1d**, **1g**–**1i**, **1o**–**1r**, **1t**, **1u**: ≥99% *ee*; **1j**: 98% *ee*; **1l**: 96% *ee*; **1m**: ≥ 95% *ee*; **1n**: 95% *ee* (chiral HPLC against racemic reference samples; see Supporting Information). The relative stereochemistry of **1** was determined according to Kobayashi et al.[7b] (see Supporting Information, Table S3).

(*R*)-**10** and (*S*)-**11** are readily available in enantiopure form from the bulk chemical furfurylalcohol (**8**) that can be converted to (±)-**9** on kilogram scale by an acid catalyzed rearrangement carried out in a microreactor setup (Scheme 2).[9a] Boc protection leads to (±)-**9**, which was resolved on a 50 g scale with *p*-methoxyphenol (0.5 equiv) utilizing Trost's technology,[9b–d] giving rise to (*R*)-**10** (42%, >99% *ee*) and (*S*)-**11** (48%, 92% *ee*) (Scheme 2). Higher enantiopurity for (*S*)-**11** (96–98% *ee*) can be achieved lowering the amount of *p*-methoxyphenol to 0.2–0.4 equiv (Supporting Information, Table S1).

Scheme 3. One Flask Synthesis of Antitumor Agents 2 and 3 (TEI-9826)



Copper(I)-catalyzed Grignard additions to (*R*)-**10** followed by trapping of the resulting enolate with aldehydes were investigated next. Optimizing the reaction conditions[10] with respect to copper sources, ligands, and solvents (Table S2, Supporting Information) revealed that CuCN·2LiCl in THF turned out to be best, directly giving rise to **1** with excellent diastereoselectivity (≥99% *de*, Table 1), irrespective of the Grignard reagent employed (aryl-, vinyl-, and alkyl) or the aldehydes used for trapping the resulting enolates (aromatic, α,β-unsaturated or aliphatic). The level of enantioselectivity is determined by the *anti*-selectivity of the Grignard reagent in the initial conjugate addition to (*R*)-**10**, and small differences in selectivity are observed correlating with its steric bulk. Introducing a vinyl group as the smallest nucleophile investigated (**1l**–**1n**, Table 1), the enantioselectivity was ≥95% *ee*, while octyl, isopropenyl, cyclohexyl, and phenyl generally gave ≥99% *ee* with the exception of **1j** (98% *ee*).

Using this strategy, the rapid assembly of biologically active prostaglandin derivatives could be accomplished. Starting from (*R*)-**10** the antitumor agent **2**[2] is accessible in one step (Scheme 3) via addition of *n*-butylmagnesium bromide followed by trapping with heptanal. The commercial anticancer drug TEI-9826 (**3**), which has been the target of many groups,[3,11] can be assembled in unparalleled purity and step economy in a one-flask protocol from (*S*)-**11** (Scheme 3). In general, (*S*)-**11** undergoes the analogous cascade sequences (not shown) described in Table 1 for (*R*)-**10** with equally high selectivities and yields.

Pseudoguaianolides and guainanes represent the largest group among naturally occurring sesquiterpene lactones.[12] We envisioned a new strategy to these structures applying the methodology described above (Scheme 4). To accomplish this goal, lactone **14** was required, which was synthesized from the known **13**[13] by a ruthenium-catalyzed double bond isomerization.[14] The pseudoguaianolide core **16**, which should be a suitable precursor for the anti-inflammatory compound **4** (Figure 1b), was then efficiently constructed by the three-component reaction between (*R*)-**10**, isopropenylmagnesium bromide, and **14**, giving rise to **15** followed by ring closing metathesis to **16**. Noteworthy, **16** is ultimately assembled from **8** and **12**, being both derived from the renewable bulk chemical furfural. No protecting groups are required in the reaction

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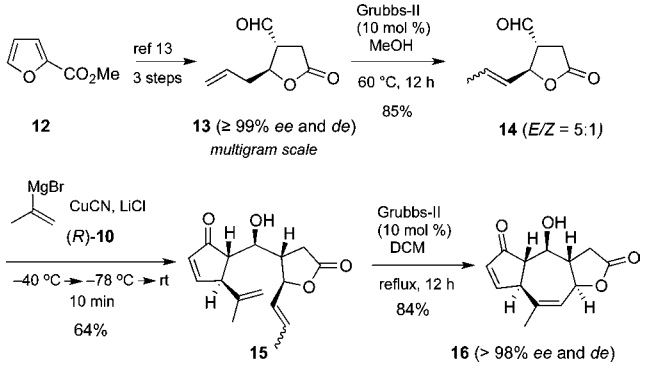
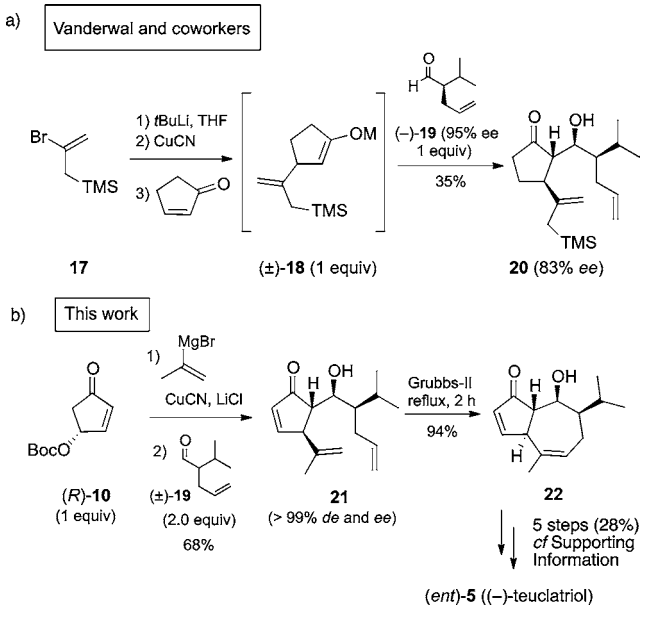
Scheme 4. Enantioselective, Protecting-Group-Free Synthesis of the Core Structure of Pseudoguaianolides



sequence, and all chiral information is introduced by catalytic asymmetric methodology (Scheme 4).

Last but not least, the enantioselective synthesis of (−)-teuclatriol (*ent*)-**5** was achieved, taking the lead from the elegant studies of Vanderwal and co-workers reported for the synthesis of (−)-teucladiol (Scheme 5).[15]

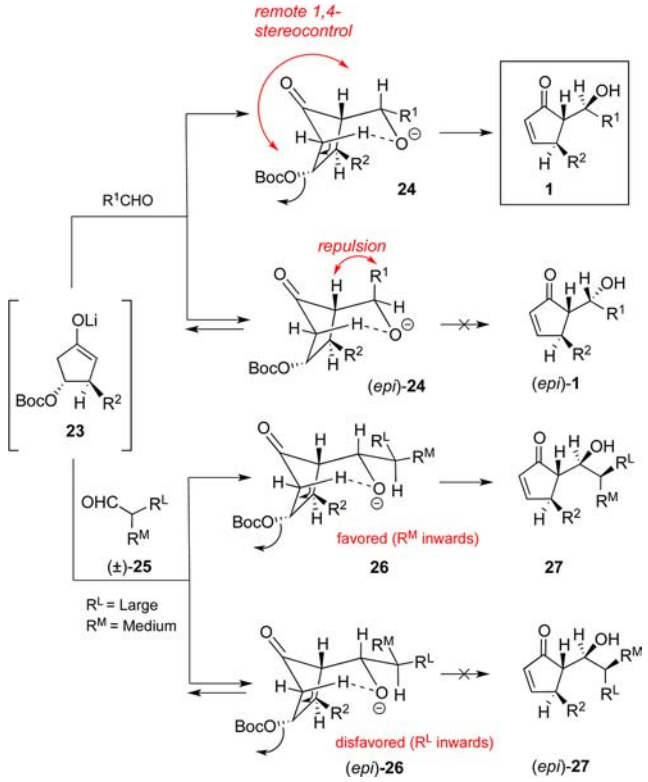
Scheme 5. (a) Kinetic Resolution of Achiral Enolate (±)-18 Using Enantiopure Aldehyde (−)-19; (b) Kinetic Resolution of α-Chiral Aldehyde (±)-19 by the Enantiopure Enolate Derived from (*R*)-10 after Addition of *i*-PrMgBr



In their key step (Scheme 5a), the kinetic resolution of racemic enolate (±)-(**18**) with enantioenriched, highly unstable aldehyde (−)-**19** was demonstrated, leading to **20**. Besides other diastereomers being formed in the crude, some erosion of enantiopurity in **20** most likely due to epimerization of aldehyde (−)-**19** was observed under the reaction conditions. The authors therefore noted that *an ideal enantioselective synthesis would incorporate enantioenriched enolate* **18**, *[but] that the asymmetric conjugate addition of* sp^2*-hybridized organometallics to cyclopentenones is not a well-developed process.*[15] We were pleased to find that (*R*)-**10** offers a solution to this problem, allowing the efficient resolution of *racemic* aldehyde (±)-**19**—much more readily available than in its enantiopure form—again with excellent selectivity (Scheme 5b). Thus, reacting (*R*)-**10** with isopropenylmagnesium bromide and (±)-**19** gave rise to **21** in diastereo- and enantiopure form. Ring closing metathesis allowed the construction of the guaianine core **22**, from which (−)-teuclatriol **5** was obtained in five further steps (see Supporting Information) in 28% overall yield.

We attribute the excellent stereocontrol achieved for **1** at the C-1′-position to the terminating Boc-OH *anti*-elimination from intermediate **24**, which we reckon is initially formed along with (*epi*)-**24** by aldol reaction from **23** (Scheme 6). Compound **24**

Scheme 6. Stereochemical Model for the Remote 1,4-Stereocontrol of the *OBoc* Group in Enolate 23



can adopt a favorable conformation that triggers elimination to **1**, while, in (*epi*)-**24**, the conformation that is required to invoke Boc-OH elimination suffers from steric repulsion caused by the axial position of R^1. Thus, assuming reversibility of the aldol process leading to **24**/(*epi*)-**24**, the OBoc-group ultimately acts as a traceless, 1,4-stereoinducing element.

This mechanistic proposal is corroborated by comparing the stereochemical outcome in the reaction of (*R*)-**10** versus (*S*)-**6** with cyclohexylmagnesium bromide followed by an aldol reaction with either benzaldehyde or *trans*-2-decanal under identical reaction conditions (Scheme 7). Extending the stereochemical model to α-chiral aldehydes (±)-**25** suggests that **26** is favored over (*epi*)-**26**: Placing the smallest substituent (hydrogen) on the α-center axially to minimize 1,3-interactions with the cyclopentanone moiety allows R^L in **26** to orient away from the chair conformation, being most favorable to trigger the elimination of Boc-OH (Scheme 6).

In conclusion, the readily available (*R*)-**10** and (*S*)-**11** allow the stereoselective synthesis of 2-cyclopentenones with excellent selectivity and operational simplicity, allowing the rapid assembly of natural product scaffolds with complex

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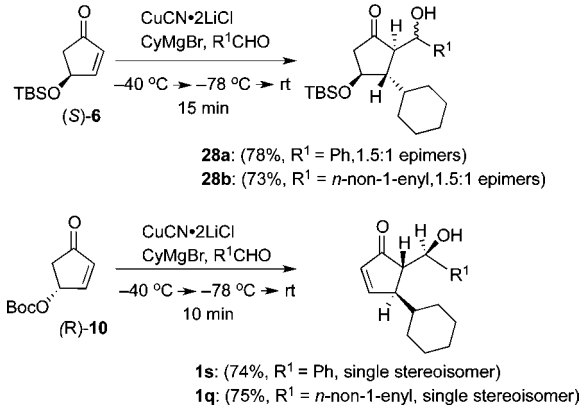
Scheme 7. Comparison of the Remote Stereoinduction of OTBS in (*S*)-6 versus OBoc in (*R*)-10



architecture. The methodology described here offers a versatile approach for the asymmetric synthesis of chiral five-membered carbocycles, being ubiquitous constituents in natural products and drugs.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details can be found in the Supporting Information (procedures, analytical data, copies of NMR and HPLC spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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