Organic LETTERS

Letter

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Enantioselective Conversion of Achiral Cyclohexadienones to Chiral Cyclohexenones by Desymmetrization

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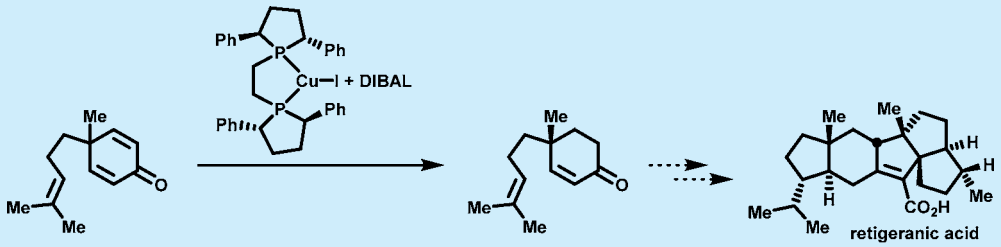
Supporting Information



ABSTRACT: The enantioselective reduction of prochiral 4,4-disubstituted 2,5-cyclohexadienones to chiral 2-cyclohexenones has been accomplished by the use of a carefully selected chiral bisphosphine–CuI complex and diisobutylaluminum hydride–hexamethylphosphoric triamide complex. This reagent has provided access to a key bicyclic intermediate for the total synthesis of the natural enantiomer of the pentacyclic sesterterpene retigeranic acid that involves spatial discrimination between CH_3 and CH_2CH_2R substituents, an operation that has been elusive previously. In addition, a second method for desymmetrization is described using catalytic enantioselective [4 + 2]-cycloaddition of cyclopentadiene to prochiral 4,4-disubstituted 2,5-cyclohexadienones.

Some years ago, we described an effective, stereocontrolled synthesis of the Himalayan lichen-derived natural product (±)-retigeranic acid (**1**, Figure 1).[1,2]

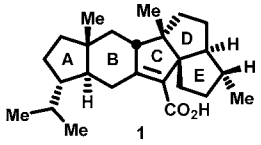
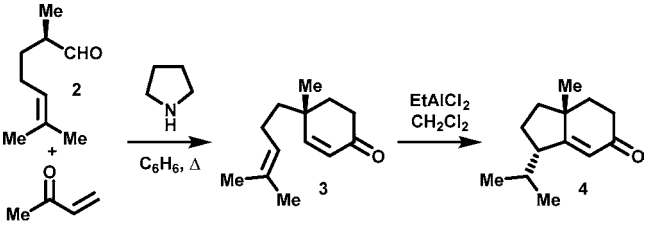


Figure 1. Retigeranic acid (**1**).

The synthesis was facilitated by the efficient synthesis[3] of the intermediates (±)-**3** and (±)-**4** starting with the cheap commercially available aldehyde **2** ("melon aldehyde") and methyl vinyl ketone, as shown in Scheme 1.

The bicyclic intermediate **4** was efficiently elaborated to the pentacyclic target (±)-**1** by the strategic application of two cycloaddition reactions. It was initially envisaged that the enantiomers of **3** might be made enantioselectively from **2** and methyl vinyl ketone using a chiral pyrrolidine derivative, thus to enable an enantioselective synthesis of retigeranic acid. Unfortunately, despite the use of a variety of chiral pyrrolidines, only modest enantioselection (ca. 1.5:1) was observed, a result that clearly was a consequence of the involvement of both *E*- and *Z*-enamines **5** and **6** in the Michael addition to methyl vinyl ketone (Figure 2).

Scheme 1. Synthesis of Intermediate 4



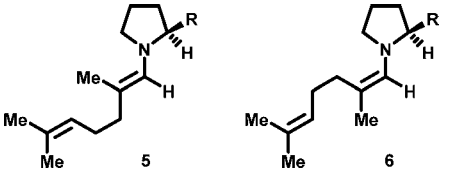


Figure 2. *E*- and *Z*-Enamines **5** and **6**.

That lack of control of *E*/*Z*-geometry can be ascribed to the nearly equal steric bulk of a methyl and methylene group and the very small energetic difference between **5** and **6**. The inability to control the *E*/*Z*-geometry in reactive enamine intermediates remains an unsolved problem.

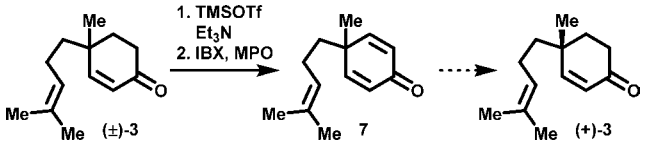
Recently, we have returned to the quest for an enantioselective synthetic route to the key chiral enone **3** with the results that are described herein. The approach which we have taken to the enantioselective synthesis of **4** involves the

Received: October 24, 2016
Published: November 18, 2016

DOI: 10.1021/acs.orglett.6b03186
Org. Lett. 2016, 18, 6172–6175

enantioselective reductive desymmetrization of the corresponding cyclohexadienone **7** which was readily prepared from **3**, as shown in Scheme 2.

Scheme 2. Oxidation/Reductive Desymmetrization Sequence for the Enantioselective Preparation of 3



The success of such a desymmetrization[4] would again depend on finding a solution to the heretofore unsolved problem of differentiation between CH_3 and CH_2CH_2R groups. Our hope was that such a distinction might be realizable by the nucleophilic addition of a Cu(I)-hydride reagent in which a bulky chiral bisphosphine ligand is bound to copper. Enantioselective Cu(I)-hydride reduction of α,β-unsaturated enones has recently been studied in detail by the Buchwald[5] and Lipshutz[6] groups.

Our initial experiments on the enantioselective reduction of **7** to (+)-**3** were conducted under the optimum conditions reported by Lipshutz et al. using the (*S*)-DTBM-SEGPHOS ligand and $Cu(OAc)_2{\cdot}H_2O$ and phenylsilane in toluene at temperatures between −78 °C and −20 °C.[6]

These reactions were slow (very slow at −78 °C) and generally required 3−5 days to achieve maximum conversion, but unfortunately the *ee* values of the enone **3** were only in the range of 35% to 50%. The other chiral bisphosphines studied gave even lower *ee*'s of **3**.[7] In view of these results, we decided to try the method developed in our laboratory several years ago involving a chiral bisphosphine, CuI, diisobutylaluminum hydride (DIBAL), and hexamethylphosphoric triamide (HMPA).[8] It was gratifying that this method afforded good results with (*S*)-DTBM-SEGPHOS (**8**, Scheme 3A) and even better results with (*R,R*)-Ph-BPE (**9**, Scheme 3B) using 10 mol % ligand and CuI in each case.[9]

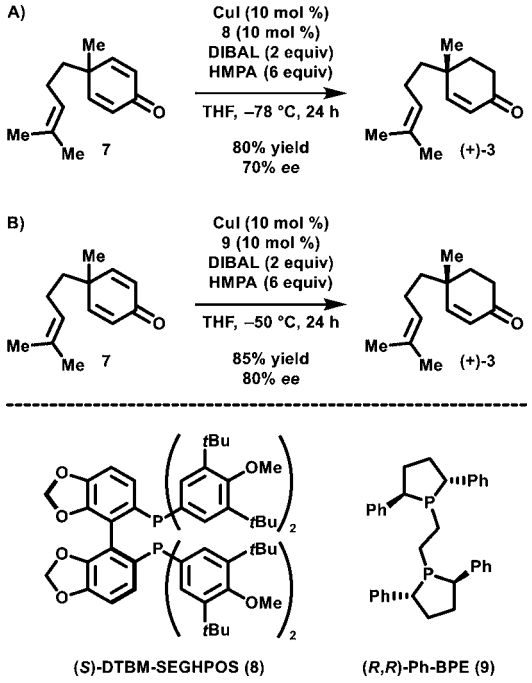
The dextrorotatory enantiomer was obtained using both (*S*)-**8** and (*R,R*)-**9**. The absolute configuration of (+)-**3** was established by cyclization with $EtAlCl_2$[3] to give the enone (−)-**4**.[10]

The ability of the Cu(I)-**9** hydride to reduce **7** to (+)-**3** with 9/1 enantioselectivity is impressive, and that encouraged us to examine a few other γ,γ-disubstituted cyclohexadienones, as discussed below. It is interesting that three-dimensional modeling studies of the addition of the Cu(I)-**9** hydride complex to dienone **7** led to the expectation that the (+)-enantiomer of **3** would be the favored product.

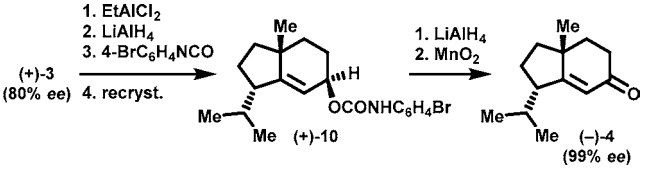
We were able to upgrade the enantiomeric purity of the chiral product (+)-**3** (obtained as described above) from 80% *ee* to 99% *ee* for the cyclization product (−)-**4** by the process outlined in Scheme 4, or simply by chromatography on a chiral OD-H column.

Cyclization of (+)-**3** to (−)-**4**, followed by diastereoselective reduction ($LiAlH_4$ in ether at −25 °C) and reaction with 4-bromophenylisocyanate and Et_3N in ether, gave the solid 4-bromophenylcarbamate (+)-**10** which could be purified by recrystallization with ether−hexanes (25:1) to afford product of 99% *ee*, mp 129−130 °C, $[\alpha]_D^{23}$ = +34.5 (*c* = 0.82, $CHCl_3$). Reductive cleavage ($LiAlH_4$ in THF at reflux) gave the corresponding 2-cyclohexenol which upon treatment with

Scheme 3. Reductive Desymmetrization of 7 Using (A) (*S*)-DTBM-SEGPHOS (8) and (B) (*R,R*)-Ph-BPE (9)



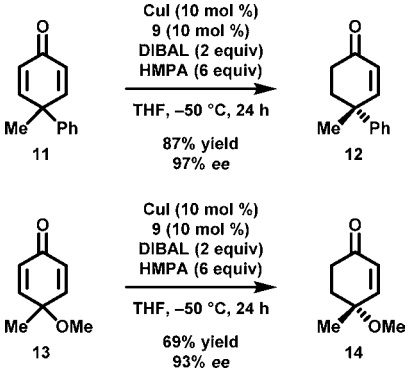
Scheme 4. Upgrade of Enantiomeric Purity from (+)-3 to (−)-4



MnO_2 in CH_2Cl_2 gave pure enone (−)-**4**, $[\alpha]_D^{23}$ = −145.7 (*c* = 0.51, $CHCl_3$) of 99% *ee* by HPLC analysis on a Chiralcel OD-H column.

The enantioselective reduction using the Cu(I)-**9** hydride reagent from DIBAL and CuI was also applied to the cyclohexadienones **11** and **13** with the results indicated in Scheme 5. The very high enantioselectivity of the desymmetrization **11** → **12** is understandable in view of the large difference in the size of methyl and phenyl substituents.[11] More surpising is the degree of enantioselectivity in the formation of the γ-methyl-γ-methoxy enone **14**.

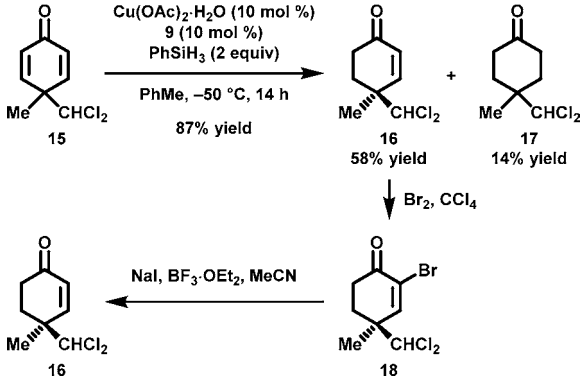
Scheme 5. Desymmetrization of Dienones 11 and 13



DOI: 10.1021/acs.orglett.6b03186
Org. Lett. 2016, 18, 6172−6175

We have also studied the selective reduction of the long known prochiral cyclohexadienone **15** (made from $CHCl_3$, *p*-cresol, and aqueous NaOH),[12] with surprising results. First, the reduction of **15** is less enantioselective using DIBAL-HMPA as a reductant rather than $PhSiH_3$, with Cu(I)-**9** as the copper-hydride source, even though the rate of reduction was considerably faster than had been observed with the dienone **7** (Scheme 3), **11**, or **13** (Scheme 5). Second, the attachment of the hydride occurred to the *opposite* β-carbon of **15** relative to **7**, **11**, or **13**, as shown in Scheme 6, and resulted in the cyclohexanone **16**, along with 14% of the saturated ketone **17** (*vide infra*).

Scheme 6. Desymmetrization of Dienone 15



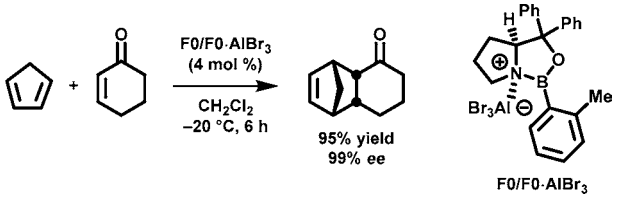
Although chromatographic separation of **16** and **17** was difficult, pure **16** was readily obtained by the sequence: (1) bromination to form **18**, which could be chromatographically separated from **17**, and (2) debromination. The enantiomeric excess of **16** obtained by the use of $PhSiH_3$ as the reductant was 77% whereas the use of DIBAL–HMPA reagent afforded product of 33% *ee*. The low enantioselectivity of the latter reaction was intriguing and could not be explained by a racemic background reaction.[13] This prompted us to investigate other means to obtain this product and also confirm the absolute configuration of the reduction product **16** by an independent method.

For this purpose, we devised an entirely different approach to the enantioselective desymmetrization of prochiral γ,γ-disubstituted cyclohexadienones which takes advantage of chiral oxazaborolidinium cationic catalysis of [4 + 2]-cycloaddition reactions,[14,15] inspired by the transformation shown in Scheme 7.[16]

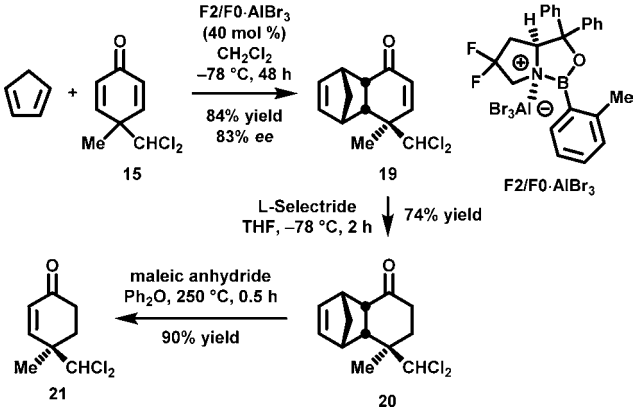
The analogous cycloaddition of cyclopentadiene to the cyclohexadienone **15** proceeded to give the adduct **19** in good yield and with good stereoselectivity[17] using our second-generation F2/F0·$AlBr_3$ catalyst,[14c] as shown in Scheme 8.

The chiral adduct **19** could be selectively reduced at the α,β-double bond by L-Selectride and then thermolyzed to provide

Scheme 7. Enantioselective [4 + 2]-Cycloaddition



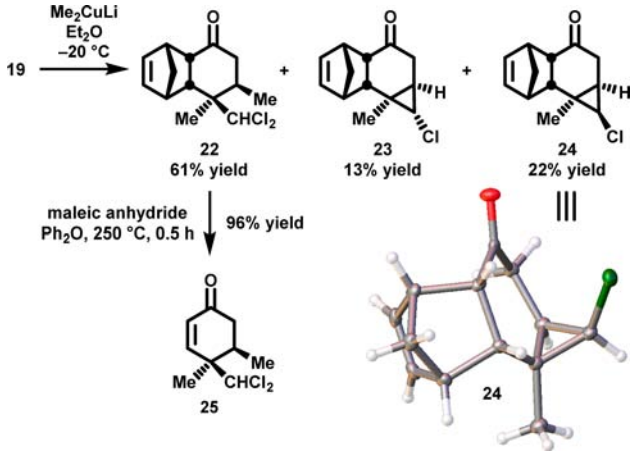
Scheme 8. Enantioselective Desymmetrization of 15 by [4 + 2]-Cycloaddition



the chiral 2-cyclohexenone **21** by a retro-Diels–Alder reaction. The optical rotation of **20**, and thus the absolute configuration, was *opposite* to the product **16** from Cu(I)-**9** hydride reduction of **15**, a fact which was further supported by chiral GC analysis of both products.

Furthermore, the enone in enantioenriched adduct **19** lends itself to further stereoselective transformations, exemplified by methyl cuprate addition to afford ketone **22** as a single diastereomer, which underwent a retro-Diels–Alder reaction to give functionalized enone **25** (Scheme 9).[18]

Scheme 9. Conjugate Addition to Enone 19 and Crystal Structure of Chlorocyclopropane 24



The desired conjugate addition product **22** was accompanied by two diastereomeric tetracylic monochlorocyclopropanes **23** and **24** which were separable by careful column chromatography.[19] Unambiguous proof of the absolute configuration of the tricyclic adduct **19**, expected from the established Diels–Alder pretransition state model,[14b] was achieved by X-ray crystallographic analysis of **24**.

The oxazaborolidinium-catalyzed [4 + 2]-cycloaddition of cyclopentadiene with cyclohexadienones represents another, complementary approach for their desymmetrization.

As a result of these studies, the absolute configuration of the quaternary carbon of enone **16** from the Cu(I)-**9** hydride reduction is thus assigned (*S*). The low enantioselectivity in this reaction in combination with the opposite sense of stereo-

DOI: 10.1021/acs.orglett.6b03186
Org. Lett. 2016, 18, 6172–6175

induction observed in the reductions of **7**, **11**, and **13** is intriguing and deserving of further investigation.

In summary, we have developed a novel method to desymmetrize γ,γ-disubstituted cyclohexadienones to chiral cyclohexenones utilizing the Cu(I)-**9** complex and DIBAL–HMPA as the reductant. The method exerts effective stereocontrol even in the challenging differentiation between a methyl (CH_3) and methylene (CH_2CH_2R) group and enables the asymmetric formal synthesis of the natural enantiomer of retigeranic acid. Additionally, when faced with an unexpectedly low *ee* in the reduction of dichloromethane-substituted substrate **15**, we demonstrated the applicability of oxazaborolidinium-catalyzed [4 + 2]-cycloadditions for the purpose of desymmetrizing cyclohexadienones. The Diels–Alder adduct thus obtained could be further exploited to stereoselectively obtain chiral 3,4,4-trisubstituted cyclohex-2-en-1-ones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03186.

Crystallographic data for compound **24** (CIF)
Experimental procedures and characterization data for all reactions and products (PDF)
Copies of ^1H and ^{13}C NMR spectra, chiral HPLC and GC traces (PDF)
X-ray crystallographic data for compound **24** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Pfizer Inc. for a research grant. Y.H. acknowledges support from Prof. Zhen Yang and Prof. Jiahua Chen of Peking University. S.B. acknowledges a postdoctoral fellowship from the Swiss National Science Foundation.

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(7) See Supporting Information for details.

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(9) *Typical experimental procedure*: To a flask containing CuI (8.0 mg, 42 μmol) and (*R,R*)-Ph-BPE (23 mg, 42 μmol) under an atmosphere of argon was added degassed THF (3.0 mL), and the suspension was sonicated for 20 min to obtain a clear solution. Then, HMPA (0.44 mL, 2.5 mmol) was added and the solution was cooled to −78 °C before DIBAL (1 M in DCM, 0.84 mL, 0.84 mmol) was added. After 10 min, dienone **7** (80 mg, 0.42 mmol) was added and the reaction was warmed to −50 °C. When the substrate was fully converted as judged by TLC, saturated aqueous NH_4Cl (5 mL) and saturated aqueous Rochelle salt (5 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, hexanes/ethyl acetate 50:1) afforded the enone (+)-**3** (68 mg, 85% yield, 80% *ee*) as a colorless oil.

(10) Paquette, L. A.; Heidelbaugh, T. M. *Synthesis* **1998**, *1998*, 495–508.

(11) Notably, the procedure described herein affords higher enantioselectivity in the reaction **11**→**12** compared to a recently reported rhodium-catalyzed conjugate reduction; see: Naganawa, Y.; Kawagishi, M.; Ito, J.-I.; Nishiyama, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 6873–6876.

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(13) Treatment of **15** with DIBAL (2 equiv) and HMPA (6 equiv) in THF at −50 °C afforded unreacted starting material after 14 h.

(14) (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100–2117. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667. (c) Reddy, K. M.; Bhimireddy, E.; Thirupathi, B.; Breitler, S.; Yu, S.; Corey, E. J. *J. Am. Chem. Soc.* **2016**, *138*, 2443–2453. (d) Thirupathi, B.; Breitler, S.; Reddy, K. M.; Corey, E. J. *J. Am. Chem. Soc.* **2016**, *138*, 10842–10845.

(15) For a similar, organocatalyzed reaction, see: Takagi, R.; Nishi, T. *Org. Biomol. Chem.* **2015**, *13*, 11039–11045.

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(17) The product was obtained as a single diastereomer with complete *endo*-selectivity, as judged by ^1H NMR and NOE studies.

(18) This approach affords the product with *cis*-relationship between the larger $CHCl_2$-group and the incoming nucleophile as determined by NOE studies. This is complementary to the *anti*-addition product obtained from conjugate addition to dienone **15**; see: ref 12c).

(19) The relative stereochemistry of these products was independently established by NOE.

DOI: 10.1021/acs.orglett.6b03186
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