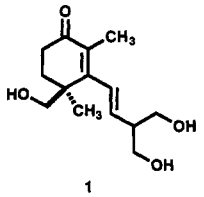
Demonstration of the Synthetic Power of Oxazaborolidine-Catalyzed Enantioselective Diels–Alder Reactions by Very Efficient Routes to Cassiol and Gibberellic Acid

E. J. Corey,* Angel Guzman-Perez, and Teck-Peng Loh

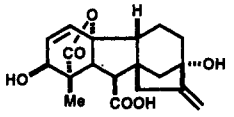
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received January 21, 1994

One of the most intensely studied areas in chemical synthesis at present is the development of new catalytic and highly enantioselective processes, especially for the most powerful synthetic constructions such as the Diels–Alder reaction.[1] Among the many promising recent advances is the use of oxazaborolidines derived from *N*-(*p*-tolylsulfonyl)tryptophan as cheap, recyclable, and very efficient catalysis of the Diels–Alder reaction of 2-substituted acroleins with dienes such as cyclopentadiene, isoprene, and furan.[2-5] Although these highly enantioselective reactions are of fundamental significance, they leave open the question of whether this methodology can be applied to the synthesis of complex molecules which require more elaborate diene components. This paper describes a number of advances in the catalytic technology which broaden its range significantly, as shown by the highly enantioselective total synthesis of two structures of unusual interest: (1) the potent but rare antiulcer substance cassiol (**1**) and (2) the plant growth regulator gibberellic acid (**2**).



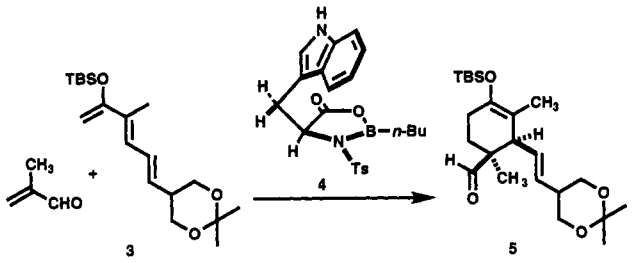
1



2

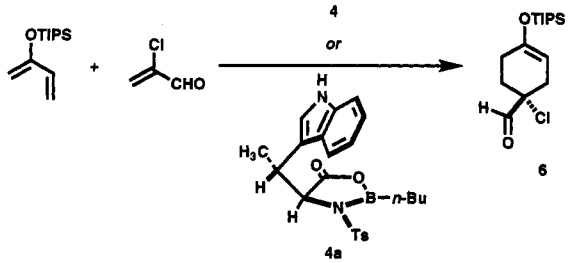
Cassiol (**1**),[6] obtained in *ca.* 0.0001% yield by extraction of the stem bark of the Chinese cinnamon (*Cinnamum cassia* Blume) followed by glycosidic cleavage, shows remarkable antiulcer activity (ED_{50} < 0.1 mg/kg for serotonin-induced rat gastric ulcer) and is an interesting therapeutic candidate. Because of the scarcity of **1**, there is a need for a short, economical synthetic route.[7,8] A short synthesis of cassiol proceeding in *ca.* 40% overall yield was developed as follows.

Initial experiments on the Diels–Alder reaction of the (*tert*-butyldimethylsilyl)oxy (TBSO) diene **3** with 2-methylacrolein catalyzed by 10–50 mol % of oxazaborolidine **4** (in CH_2Cl_2 at −78 °C for 48 h) afforded discouraging results since the adduct **5** was obtained in up to 90% yield but with only 6% enantiomeric excess (ee).[9] Nonetheless, further research on this Diels–Alder process revealed that a set of four critical modifications could be made which together result in high enantioselectivity. First, it



3 **5**

was discovered that TBSO or MeO substituents on the diene component are definitely deleterious to enantiocontrol by catalyst **4**, possibly because they favor very asynchronous or two-step pathways. For example, 2-TBSO-butadiene and 2-MeO-butadiene undergo Diels–Alder reaction with 2-halo- or 2-methylacrolein with **4** as catalyst at −78 °C in CH_2Cl_2 to afford Diels–Alder adducts of only 50–70% ee (*cf.* 92% ee for the corresponding reactions with isoprene). In contrast, it was discovered that ((triisopropylsilyl)oxy) (TIPSO)-1,3-butadienes react with much higher enantioselectivity under the same conditions; for instance, 2-TIPSO-butadiene, 2-chloroacrolein, and 10 mol % of catalyst **4** at −78 °C in CH_2Cl_2 produce Diels–Alder adduct **6** of 94% ee. Second, it was found that the (*R*)-β-methyl catalyst **4a**[3,4] led to adduct **6** with even higher enantioselectivity (97% ee) under the same conditions. Third, it appears from molecular modeling that



4a **6**

in the case of 1-substituted dienes, such as **3**, there is probably considerable steric repulsion in the transition state between the C(1) substituent and the group attached to boron and that the optimal catalyst system should contain a hydrogen substituent on boron rather than alkyl. Finally, we discovered by experimentation that the use of a 1:1 mixture of toluene and methylene chloride as solvent frequently leads to significantly higher enantioselection than CH_2Cl_2 itself with electron-rich dienes.[10]

With this new information, the synthesis of cassiol, which is outlined in Scheme 1, was achieved with very high enantioselectivity. Wittig coupling of aldehyde **7**[11] and phosphonium ylide **8**[12] produced a mixture of γ,δ-*trans* and γ,δ-*cis* dienes (86%, ratio 1.7:1), which upon isomerization with I_2 and chromatography on silica gel afforded *ca.* 90% of *trans,trans* diene **9** and fractions containing the *trans,cis* diene which can be isomerized and recycled. Deprotonation of **9** and silylation with TIPS triflate gave the *E,E*-triene **10** in >99% yield. The Diels–Alder reaction of **10** and 2-methylacrolein in the presence of 25 mol % of catalyst **11**[3,4] in 1:1 CH_2Cl_2–toluene at −78 °C for 42 h afforded adduct **12** in 83% yield and 97% *ee with complete position and diastereoselectivity* (none of the diastereomer with formyl and vinyl substituents *trans* to one another could be detected by NMR or chromatographic analysis).[13] Conversion of the Diels–Alder

(1) For recent reviews, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (b) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. (c) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

(2) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.

(3) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290.

(4) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979.

(5) Corey, E. J. *Abstr. Natl. Org. Chem. Symp., 33rd* **1993**, 30.

(6) Shiraga, Y.; Okano, K.; Akira, T.; Fukaya, C.; Yokoyama, K.; Tanaka, S.; Fukui, H.; Tabata, M. *Tetrahedron* **1988**, *44*, 4703.

(7) For a recent discussion of plant-derived antiulcer compounds, see: Lewis, D. A. *Chem. Br.* **1992**, 141.

(8) Two syntheses of **1** have been reported to date. The first by the original Green Cross Corp. group requires an expensive chiral starting material and a 15-step route, see: Takemoto, T.; Fukaya, C.; Yokoyama, K. *Tetrahedron Lett.* **1989**, *30*, 723. The second synthesis commences with a chiral β-hydroxy acid produced by a yeast reduction and involves 11 steps and an overall yield of 5.6%, see: Uno, T.; Watanabe, H.; Mori, K. *Tetrahedron* **1990**, *46*, 5563.

(9) All reaction temperatures are reported in °C.

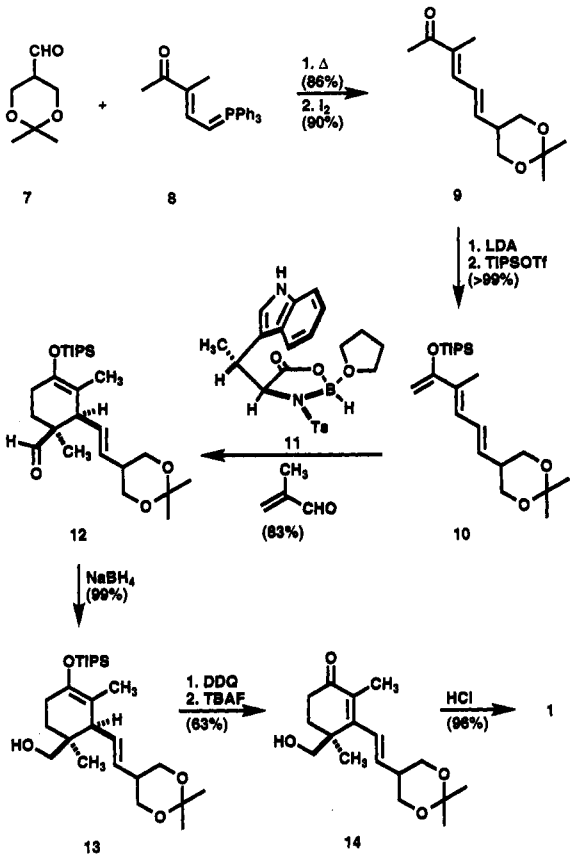
(10) Extensive studies have revealed that *p*-tolylsulfonyl is the optimum *N*-substituent in the catalyst structure; additional details will be published elsewhere.

(11) Aldehyde **7** was prepared in 70% yield by DIBAL-H reduction (toluene, −78 °C, 2 h) of the corresponding ester, which has been reported previously: Bates, H. A.; Farina, J.; Tong, M. *J. Org. Chem.* **1986**, *51*, 2637.

(12) The known ylide **8** was prepared from crotyltriphenylphosphonium bromide by deprotonation (2.6 equiv of lithium hexamethyldisilazide in THF), reaction with 1.5 equiv of acetyl chloride, and recrystallization from ether, see: Zbiral, E.; Berner-Fenz, L. *Tetrahedron* **1968**, *24*, 1363.

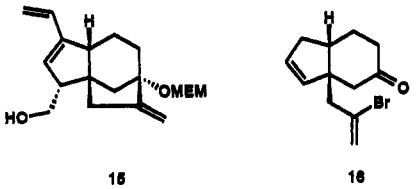
0002-7863/94/1516-3611$04.50/0

Scheme 1



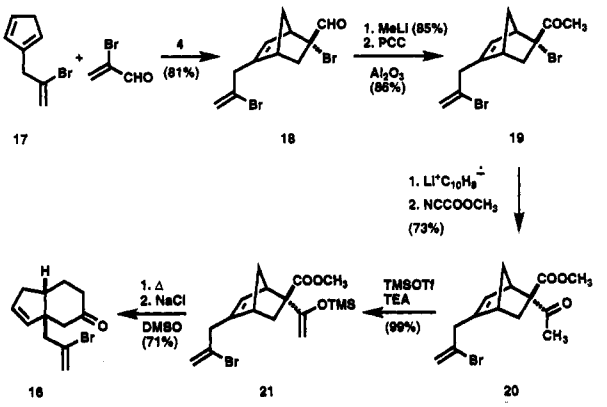
adduct **12** to cassiol was accomplished by the sequence: (1) borohydride reduction to the corresponding alcohol **13** (1:1 THF–H_2O, 0 °C, 15 min, 99%), (2) oxidation with 6 equiv of DDQ (CH_2Cl_2 containing 2 equiv of hexamethyldisilazane at 23 °C for 3 h and desilylation (*n*-Bu_4NF, THF, 23 °C, 15 min) to form **14** (65% from **13**, possibly not optimal), and (3) deketalization (5 mM HCl in MeOH at 23 °C for 30 min, 96%) to form **1**, $[\alpha]^{20}_D$ + 8.5° (*c* = 0.27, MeOH), which was spectroscopically and chromatographically identical with the natural product.

The first total synthesis of gibberellic acid (**2**) was accomplished via the key intermediate (±)-**15**,[14,15] which could be made expeditiously from (±)-**16**,[16] in a route which involved a subsequent resolution step. We now describe an efficient enantioselective route to chiral **16** which establishes the first catalytic enantioselective synthesis of gibberellic acid, as shown in Scheme 2.



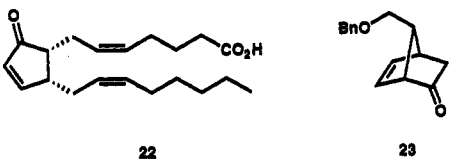
Reaction of 2-(2-bromoallyl)-1,3-cyclopentadiene[16,17] (**17**) and 1.05 equiv of 2-bromoacrolein in the presence of 10 mol % of catalyst **4** at −78 °C in CH_2Cl_2 for 16 h produced after chromatography on silica gel the desired adduct **18** in 81% yield

Scheme 2



and 99% ee (*exo*/*endo* ratio 99:1).[18] Reaction of **18** with 1.5 equiv of methyllithium in ether at −78 °C for 2 h afforded the corresponding secondary alcohol (85%), which upon treatment with pyridinium chlorochromate on Al_2O_3 (5 equiv) in CH_2Cl_2 at 23 °C for 3 h provided the liquid α-bromo ketone **19** (86%), $[\alpha]^{23}_D$ +68.3° (*c* = 5.5, THF). Conversion of **19** to the enolate by reductive debromination with 2 equiv of lithium naphthalenide in THF at −78 °C followed by immediate treatment with methyl cyanoformate[19] gave the liquid keto ester **20** stereospecifically in 73% yield after chromatography on silica gel. Transformation of **20** to the trimethylsilyl enol ether **21** (4 equiv of Et_3N and 2 equiv of TMS triflate at 0 °C for 15 min and 23 °C for 1 h; 99% yield), heating at 160 °C in toluene containing propylene oxide to effect Cope rearrangement,[16] and treatment of the resulting β-keto ester with wet NaCl in dimethyl sulfoxide at 125 °C for 4 h to effect decarboxylation[16] provided after chromatography on silica gel the *cis* hydrindenone **16**, $[\alpha]^{23}_D$ + 3.6° (*c* = 2.5, $CHCl_3$) in 71% yield. Chiral intermediates **20**, **21**, and **16** were spectroscopically identical with the racemic compounds described earlier.[16]

The methodology used for the synthesis of **16** (using catalyst **4a**) has also been applied to the catalytic enantioselective synthesis of preclavulone A **22** (99% ee)[20] and the valuable prostaglandin precursor **23** (99% ee).[2,21,22]



The findings reported herein provide critical information for more extensive applications of catalytic enantioselective Diels–Alder methodology to a range of complex molecules.[23]

Supplementary Material Available: Experimental and characterization data for new compounds (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) Enantioselectivity was determined by HPLC analysis of transformation product **14** using a Chiralpak AD column, 92.5:7.5 hexane–isopropyl alcohol, at 23 °C with detection at 268 nm; elution times (1 mL/min flow) were 17.20 (minor) and 20.22 min (major) for the enantiomers.

(14) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalon, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8034.

(15) Corey, E. J.; Smith, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 1038.

(16) Corey, E. J.; Munroe, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 6129. Munroe, J. E. Ph.D. Dissertation, Harvard University, Cambridge, MA, 1982.

(17) Used as a 1.7:1 mixture of **17** and the less reactive 1-bromoallyl position isomer.[16]

(18) The enantiomeric excess of adduct **18** was determined, after reduction to the corresponding primary alcohol and conversion to the Mosher ester, by 500-MHz ^1H NMR analysis; found for **18**, $[\alpha]^{23}_D$ + 25.7° (*c* = 1.1, CH_2Cl_2).

(19) Mander, L. N.; Sethi, P. *Tetrahedron Lett.* **1983**, *24*, 5425.

(20) For the pathway, see: Corey, E. J.; Xiang, Y. B. *Tetrahedron Lett.* **1988**, *29*, 995.

(21) In all these processes, the *N*-tosyltryptophan derivative is easily and efficiently recoverable for reuse. The chiral prostaglandin precursor **23** is best prepared by this methodology.

(22) For an impressive recent application of the B–H analog of catalyst **4** to natural product synthesis, see: Marshall, J. A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987.

(23) This research was supported by grants from the National Science Foundation and the National Institutes of Health and a graduate fellowship to A.G.-P. from the Schering-Plough Company.