pecially with nonaromatic solvents.

Two Typical Runs. P-4VPTS (1.00 g) was added to a mixture of 1-dodecanol (932 mg, 5 mmol) and Aldrich 2,3-dihydropyran (631 mg, 7.5 mmol) in 25 mL of dry benzene (hood!). Magnetic stirring at room temperature was continued for 4 h after which the catalyst was removed by filtration and washed; the combined filtrate and washings were stripped to produce crude product. Thick-layer chromatography (Merck silica gel GF-254 type 60 with a 5:1 hexane/ether eluant) gave 2-(1-dodecyloxy)-tetrahydro-2*H*-pyran (1.28 g, 95%) as a clear liquid with satisfactory NMR, IR, and GLC data. The same procedure worked successfully on a somewhat larger scale (20 mmol of alcohol), using column chromatography.

Cholesterol (1.93 g, 5 mmol) was treated exactly as the 1-dodecanol except that the stirring lasted 6 h. Removal of the solvent gave a solid residue which was dried for 2 h under reduced pressure. Recrystallization from ethyl acetate yielded white needles (2.24 g, 95%) with a melting point of 151–152 °C (lit.[1] mp 154–155 °C).

Acknowledgment. We are grateful to the National Science Foundation, National Institutes of Health, and the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

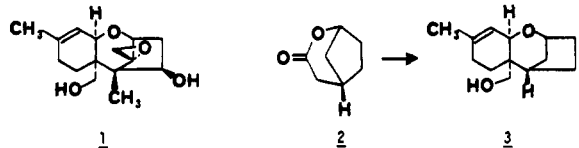
Registry No. 1-Dodecanol, 112-53-8; cyclohexanol, 108-93-0; nopol, 128-50-7; geraniol, 106-24-1; 3-acetyl-1-propanol, 1071-73-4; cholesterol, 57-88-5; benzhydrol, 91-01-0; 2-phenyl-2-propanol, 617-94-7; 1-methylcyclohexanol, 590-67-0; 1-dodecanol THP ether, 63588-79-4; cyclohexanol THP ether, 709-83-1; nopol THP ether, 79433-80-0; geraniol THP ether, 59632-99-4; 3-acetyl-1-propanol THP ether, 1012-10-8; cholesterol THP ether, 6252-45-5; benzhydrol THP ether, 79373-25-4; 2-phenyl-2-propanol THP ether, 79373-26-5; 1-methylcyclohexanol THP ether, 72347-38-7; P-4VPTS, 29323-86-2; P-2VPTS, 79373-27-6.

Communications

Synthesis of a Bicyclic Precursor to Verrucarol: Application of a Trimethylsilyl-Controlled Diels–Alder Reaction and Wagner–Meerwein Rearrangement Sequence†

Summary: A synthesis of lactone 4, which corresponds to the bicyclic nucleus of verrucarol (1), is described. The key steps of this synthesis are the $BF_3{\cdot}Et_2O$ catalyzed Diels–Alder reaction of 7 with methyl acrylate and the oxidative conversion of cycloadduct 8 into epoxy alcohols **10a** and **10b**. A trimethylsilyl group plays a crucial role in both of these transformations.

Sir: Verrucarol (1) possesses the 12,13-epoxytrichothecene skeleton common to the trichothecene family of terpene antibiotics.[1] The remarkable biological properties of many of these compounds, particularly some of the macrocyclic di and triester derivatives of verrucarol, have stimulated considerable interest in their synthesis.[2] We recently described a synthetic approach to the trichothecene ring system, exemplified by the stereospecific synthesis of 3

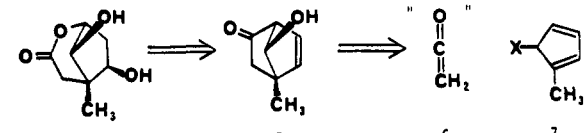


1 2 3

from lactone 2.[3] We describe herein a stereoselective synthesis of lactone 4, a bicyclic compound bearing all of the functionality necessary for elaboration to verrucarol.

Our solution to the synthetic problem posed by 4 has its genesis in the analysis summarized in Scheme I.

Scheme I



4 5 6 7

Certain structural features of 4, notably the lactone and the C-4 hydroxyl group, suggested that bicycloheptenone 5, or a suitable synthetic equivalent, might be an appropriate precursor. This, in turn, suggested a Diels–Alder construction involving a ketene equivalent, 6, and a disubstituted cyclopentadiene, 7. There are, of course, a number of obvious pitfalls to such a strategy. First, disubstituted cyclopentadienes such as 7 are not, in general, readily available. More important, the thermal stability of 7 (e.g., X = OR) relative to other tautomers would be a problem ([1,5] hydrogen shifts), except in cases where 7 could be synthesized and worked with at low temperature.[4] Finally, all known ketene equivalents[5] would be expected to add to 7, preferentially, in the undesired regiochemical sense, leading to the carbonyl-transposed isomer of 5. On the assumption that the first two problems could be solved, some means of inverting the orientational preference of 6 with an appropriate cyclopentadiene would be required, or, alternatively, some controlled means of reorganizing the functional group relationships in the initial bicycloheptene Diels–Alder adduct would need to be employed. Our synthesis of 4, which in fact follows the latter logic, involves use of 7 (X = $SiMe_3$; Scheme II). The choice of a trimethylsilyl group not only simplifies the synthesis of 7[6] but also serves to ensure a sufficient

† This communication is dedicated to Professor George H. Büchi on the occasion of his 60th birthday.

(1) Doyle, T. W.; Bradner, W. T. In "Anticancer Agents Based on Natural Product Models"; Cassidy, J. M., Douros, J., Eds.; Academic Press: New York, 1980; Chapter 2.

(2) For leading references see: (a) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825. (b) Kraus, G. A.; Frazier, K. *Ibid.* **1980**, *45*, 4820. (c) Welch, S. C.; Prakasa Rao, A. S. C.; Gibbs, C. G.; Wong, R. Y. *Ibid.* **1980**, *45*, 4077. (d) Pearson, A. J.; Ong, C. W. *Tetrahedron Lett.* **1980**, 4641. (e) Still, W. C.; Tsai, M.-Y. *J. Am. Chem. Soc.* **1980**, *102*, 3655.

(3) Roush, W. R.; D'Ambra, T. E. *J. Org. Chem.* **1980**, *45*, 3927.

(4) Such is the case with 5-alkylcyclopentadienes. See, for example: (a) Corey, E. J.; Ravindranathan, T.; Terashima, S. *J. Am. Chem. Soc.* **1971**, *93*, 4326. (b) Heck, J. V. Ph.D. Thesis, Harvard University, Cambridge, Massachusetts, 1976.

(5) Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *J. Am. Chem. Soc.* **1974**, *96*, 5261. See also ref 4a,b.

(6) (a) Davison, A.; Rakita, P. E. *Inorg. Chem.* **1970**, *9*, 289; (b) *J. Am. Chem. Soc.* **1968**, *90*, 4479.

(7) The rate of trimethylsilyl [1,5] migrations is 10^6 that of the rate of [1,5] hydrogen migrations in (trimethylsilyl)cyclopentadiene: Ashe, A. J., III. *J. Am. Chem. Soc.* **1970**, *92*, 1233.

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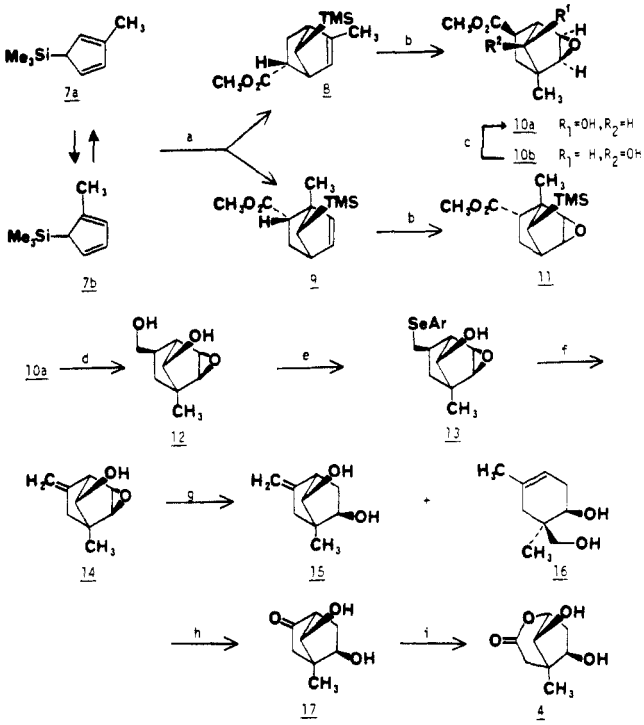
Scheme II[a]



[a] (a) methyl acrylate (1.2 equiv), $BF_3{\cdot}Et_2O$ (1.2 equiv), CH_2Cl_2, −78 °C, 2 h (90%; ratio of 8/9 = 83:17); (b) DNPBA (4–6 equiv), CH_2Cl_2, $NaHCO_3$, 23 °C, 50 h (10a, 42–51%; 10b, 10–12%; 11, 15–16%); (c) (i) TFAA, Me_2SO, −60 °C, and then Et_3N (90%); (ii) $NaBH_4$, EtOH (70%); (d) $LiAlH(OCH_3)_3$ (excess), THF, 23 °C, 1 h (93%); (e) o-nitrophenyl selenocyanate (1.1 equiv), n-Bu_3P, THF, 23 °C, 30 min (71%); (f) MCPBA (1.1 equiv), CH_2Cl_2, −10 °C, 15 min, and then i-Pr_2NH (2 equiv), 23 °C, 5–7 h (95%); (g) Li (excess), ethylenediamine, THF, 23 °C, 0.5–1 h (66% of 15); (h) O_3, CH_2Cl_2, −78 °C, and then $(CH_3)_2S$, 23 °C, 12 h (89% based upon unrecovered 15); (i) MCPBA, $NaHCO_3$, CH_2Cl_2, 23 °C, 2 h (95%).

steady-state concentration of **7a**,[7] the desired regioisomer for the purposes of this synthesis, and to control the crucial Wagner–Meerwein rearrangement (**18** → **19**).[8]

Treatment of readily available (methylcyclopentadienyl)trimethylsilane, a rapidly equilibrating mixture of isomers consisting largely of **7a** and **7b**,[6] with the $BF_3{\cdot}OEt_2$ complex of methyl acrylate in CH_2Cl_2 at −78 °C cleanly produced an 83:17 mixture, respectively, of **8**[10a,c] (deriving from **7a**) and **9**[10a] (from **7b**) in a 90% combined yield.[9] Pure samples of each isomer were obtained by preparative reverse-phase HPLC (1:1 CH_3CN–H_2O; 10-μm particle size, 7.8 mm × 30 cm Waters μ-Bondapak C_{18} Column).

It was expected[8] from the outset that peracid oxidation of **8** would afford **18**[10a,c] which, in turn, would undergo a trimethylsilyl-controlled Wagner–Meerwein rearrangement to **19**[10a,c] on exposure to a Lewis acid. This indeed proved to be the case. However, oxidation of **8** with $NaHCO_3$–buffered MCPBA proved to be quite sluggish; in one instance, 59% of **18**, 20% of **8**, and small amounts (<10%) of **10a** were obtained from 2-day reaction. Oxidation of **8** with an excess of the more reactive 3,5-dinitroperoxybenzoic acid[11] (DNPBA; CH_2Cl_2, buffered with suspended $NaHCO_3$) was comparably slow, but in this instance a mixture of the highly oxidized, rearranged, epoxy alcohol **10a**[10a,b,c] (69%) and its epimer **10b**,[10a,c] (mp 93–94 °C, 19%) were obtained. The rearrangement of **18** to **19** and the epoxidation of **19** to **10a** thus occur under these reaction conditions. The presence of **10b** presumably reflects a low degree of stereoselectivity in the DNPBA oxidation of **8**, since subjection of **18** to the aforementioned reaction conditions afforded **10a** (71%) as the sole epoxy alcohol product. The epimeric relationship of **10a** and **10b** was established by oxidation of **10b** with a Swern reagent[12] [(1) TFAA, Me_2SO, −60 °C; (2) Et_3N (90%)] followed by $NaBH_4$ reduction which afforded **10a**, uncontaminated with **10b**, in 63% overall yield.

For large-scale work, it proved unnecessary to separate the mixture of Diels–Alder adducts **8** and **9**. Thus, oxidation of this mixture with DNPBA, as above, afforded an easily separated mixture of **10a** (42–51%), **10b** (10–12%), and epoxysilane **11** (15–16%), which derives from **9** but which does not rearrange under the reaction conditions. Reduction of **10a** to the crystalline alcohol **12**,[10a,b] (mp 79–81 °C) was accomplished by using $LiAlH(OCH_3)_3$ (93% yield).[13] Treatment of **12** with o-nitrophenyl selenocyanate and n-Bu_3P in THF afforded the golden selenide **13**:[10a,b] mp 109.5–110.5 °C; 71% yield.[14] Oxidation of **13** with MCPBA (CH_2Cl_2, −10 °C) followed by selenoxide elimination in the presence of diisopropylamine[15] afforded the extremely volatile olefin **14**[10a,c] (95%). Treatment of **14** with Li in ethylenediamine (THF, 23 °C)[16] afforded the crystalline diol **15**[10a,b] (mp 97–98 °C) uncontaminated with its regioisomer[17] in 66% yield. Under these conditions, however, **15** was also converted to **16**:[10a] mp 76 °C; 5–8% yield. Ozonization of **15** produced **17**[10a,c] (mp 100–101 °C; 89% yield based on unrecovered olefin), Baeyer–Villiger oxidation of which afforded **4**:[10a,b] mp 180–184 °C; 93% yield.

Assignment of structures throughout this sequence is based on extensive spectroscopic characterization. Particular emphasis was placed on the 250-MHz proton NMR spectrum, which in conjunction with homonuclear decoupling experiments provided assignments consistent with the wealth of data available for this class of compounds.[18] Also consistent with these assignments is the observation that treatment of dibenzoate **20**[10a] with LDA in THF at

(8) Fleming, I.; Michael, J. P. *J. Chem. Soc., Chem. Commun.* **1978**, 245.

(9) This product ratio was not affected significantly by conducting the reaction at lower temperatures (-95 °C). The ratio of Diels–Alder adducts from **5a** and **5b**, however, is very much a function of the dienophile and choice of reaction conditions. A more detailed study of the Diels–Alder reactions of **7** will be reported in due course.

(10) (a) All new compounds were fully characterized by NMR, IR, and mass spectroscopy. (b) A satisfactory combustion analysis (±0.3%) was obtained for this compound. (c) The elemental composition of this compound was verified by a precise mass measurement.

(11) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.

(12) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.

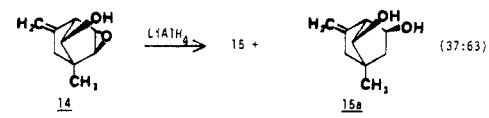
(13) Brown, H. C.; Weissman, P. M. *J. Am. Chem. Soc.* **1965**, *87*, 5614.

(14) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(15) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.

(16) Brown, H. C.; Ikegami, S.; Kawakami, J. H. *J. Org. Chem.* **1970**, *35*, 3243.

(17) $LiAlH_4$ reduction of **14** afforded a 37:63 mixture of **15** and **15a**.



(18) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, 1972; 1975; pp 288–289, 334–335, and references therein.

20 21

-78 °C for 20 min produced an approximate 1:1 mixture of **20** and cyclopropane **21**[10a].

Elaboration of lactone **4** to verrucarol is under current investigation and will be reported upon in due course.

Acknowledgment. This research was supported by a grant from the National Cancer Institute (Grant No. CA 26830). We are grateful to Dr. Catherine Costello for measurement of high-resolution mass spectra.

Registry No. **4**, 79410-03-0; **7a**, 79410-04-1; **7b**, 79410-05-2; **8**, 79410-06-3; **9**, 79410-07-4; **10a**, 79410-08-5; **10b**, 79464-62-3; **11**, 79420-95-4; **12**, 79410-09-6; **13**, 79410-10-9; **14**, 79410-11-0; **15**, 79410-12-1; **15a**, 79410-13-2; **16**, 79410-14-3; **17**, 79410-15-4; **18**, 79410-16-5; **19**, 79410-17-6; **20**, 79410-18-7; **21**, 79410-19-8.

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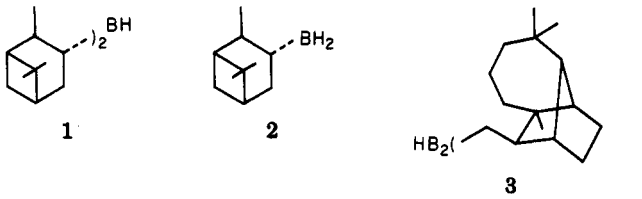
High Asymmetric Induction in the Chiral Hydroboration of Trans Alkenes with Isopinocampheylborane. Evidence for a Strong Steric Dependence in Such Asymmetric Hydroborations

Summary: Isopinocampheylborane, $IpcBH_2$ (**2**), achieves asymmetric hydroboration of trans-disubstituted alkenes with exceptionally high asymmetric induction. The product alcohols, obtained after oxidation of the intermediate organoboranes, exhibit enantiomeric purities in the range of 70–92% ee. The enantiomeric purities of the products increase with the increasing steric requirement of the alkyl substituent in the trans-disubstituted alkene.

Sir: Diisopinocampheylborane, Ipc_2BH (**1**), is a chiral hydroborating agent with very large steric requirements.[1] It hydroborates prochiral olefins with very low steric requirements such as 2-methyl-1-alkenes to provide optically active products in the range of 5–30% ee.[2] It is exceptionally effective with cis-disubstituted alkenes with considerably higher steric requirements,[3] achieving asymmetric synthesis as high as 98.4% for *cis*-2-butene.[4] Unfortunately, it fails with olefins of still higher steric requirements such as trans-disubstituted alkenes[5] and trisubstituted alkenes.[5]

We recently discovered that trisubstituted alkenes are handled satisfactorily by chiral hydroborating agents of lower steric requirements, isopinocampheylborane, $IpcBH_2$ (**2**),[6,7] and dilongifolylborane, Lgf_2BH (**3**).[8]



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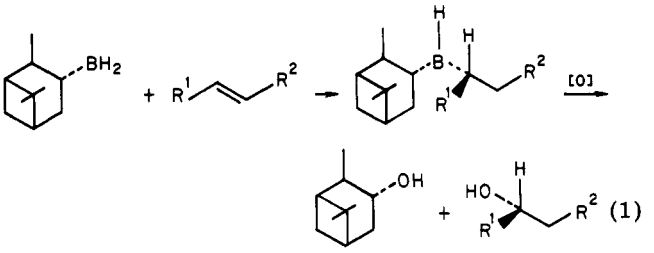
With these reagents, appropriate trisubstituted alkenes could be converted into optically active products in the range of 52–100% ee. Only the large class of trans-disubstituted alkenes has not yet been successfully transformed into optically active products by asymmetric hydroboration.

An attempt to apply dilongifolylborane to *trans*-2-butene was unsatisfactory, yielding 2-butanol, after oxidation, of only 26% ee.[9] However, $IpcBH_2$ was far more favorable, yielding 2-butanol of 73% ee (eq 1; $R^1 = R^2 = CH_3$).



(1)

This experiment encouraged us to explore the application of $IpcBH_2$ to a number of representative trans-disubstituted alkenes: *trans*-3-hexene (eq 1; $R^1 = R^2 = C_2H_5$), *trans*-2,2,5,5-tetramethyl-3-hexene (*trans*-di-*tert*-butylethylene; eq 1; $R^1 = R^2 = C(CH_3)_3$), *trans*-2-pentene (eq 1; $R^1 = CH_3$, $R^2 = C_2H_5$), and *trans*-1-phenyl-1-propene (eq 1; $R^1 = Ph$, $R^2 = CH_3$). In all cases the asymmetric hydroboration proved satisfactory. Oxidation produced the corresponding alcohols with optical activities in the range of 70–92% ee. The results are summarized in Table I.

The reagent, $IpcBH_2$, preferentially attacks from the bottom enantiotopic face of the *trans*-alkene (eq 1) to provide product alcohols of the same absolute configuration. It should be noted that (+)-2,2,5,5-tetramethyl-3-hexanol and (+)-1-phenyl-1-propanol have an *R* notation because of the change in priority of the substituents on the chiral carbon atom. However, these products have an absolute configuration related to that of the other alcohols listed in Table I.

The importance of the steric factor is indicated by the increase in the optical purity of the product in proceeding from *trans*-2-butene ($R = CH_3$) or *trans*-3-hexene ($R = C_2H_5$) to *trans*-di-*tert*-butylethylene ($R = C(CH_3)_3$).

It is also of interest to note the range in the effectiveness of diisopinocampheylborane, a hydroborating agent of large steric requirements, and isopinocampheylborane, a hydroborating agent of low steric requirements (Table II).

The experimental procedure follows. All operations were carried out under nitrogen. TMED·2$IpcBH_2$ was prepared by following the reported procedure.[10] A 0.6 M solution of TMED·2$IpcBH_2$ was made in THF. To 53.3 mL (32 mmol) of this solution was added 7.9 mL (64 mmol) of boron trifluoride etherate at 25 °C. The reaction mixture was stirred at 25 °C for 1.25 h. The solution containing

(1) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486.
(2) Zweifel, G.; Ayyangar, N. R.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 1076.
(3) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 397.
(4) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1977**, *15*, 12.
(5) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 1071.
(6) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 5514.
(7) Mandal, A. K.; Jadhav, P. K.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 3543.
(8) Jadhav, P. K.; Brown, H. C. *J. Org. Chem.* **1981**, *46*, 2988.
(9) Jadhav, P. K.; Brown, H. C., to be submitted for publication.
(10) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.

0022-3263/81/1946-5047$01.25/0