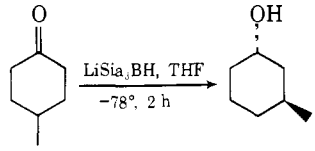
quantitative yield by the addition of 1 mole equiv of *tert*-butyllithium[7] in *n*-pentane (0°) to a tetrahydrofuran (THF) solution of trisiamylborane[8] at −78°; ^{11}B NMR (BF_3:Et_2O) exhibits two pairs of doublets at +13.28 (three parts), J = 75 Hz and +14.48 (one part), J = 75 Hz.[9] Analogously lithium tris(*trans*-2-methylcyclopentyl)borohydride is prepared in 100% yield.

Lithium trisiamylborohydride completely reduces the moderately hindered ketones, 2-methylcyclopentanone and 2-methylcyclohexanone, to the corresponding cis alcohols in ≥99.5% stereoselectivity.

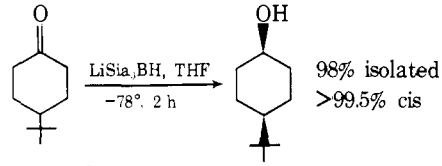
The relatively unhindered ketone, 3-methylcyclohexanone, is quantitatively reduced to *trans*-3-methylcyclohexanol in 99.6% isomeric purity (eq 2).



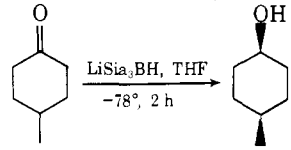
99.6% (2)

Under these conditions the corresponding reaction with L-Selectride proceeds with only 95% stereoselectivity.

Even more important is the reduction of 4-alkylcyclohexanones, the least hindered of the alkylcyclohexanones. Essentially all of the simple hydride reagents preferentially attack from the axial direction giving the *trans*-carbinol as the major product.[10] Application of L-Selectride increases the equatorial attack significantly (90–96%). We examined a representative series of 4-alkylcyclohexanones (alkyl = methyl, ethyl, isopropyl and *t*-butyl) with LTSBH. All of them underwent essentially quantitative conversion to *cis*-4-alkylcyclohexanols in 99% or better isomeric purity (eq 3 and 4). The unhindered

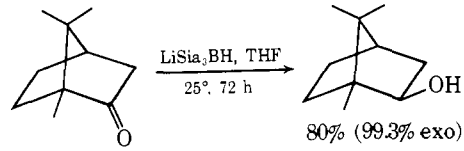


98% isolated
>99.5% cis (3)



99% (4)

bicyclic ketone, norcamphor, is reduced to the endo alcohol in 99.5% purity. Surprisingly, the highly hindered bicyclic ketone, camphor, is essentially inert to LTSBH at 0° (2 h); only 10% conversion is achieved in 24 h. However, it is possible to achieve complete conversion at higher temperature: 80% conversion, 99.3% exo, in 72 h at 25° (eq 5). The corresponding reduction



80% (99.3% exo) (5)

with LTMBH at 0° is complete in 24 h. All of the trialkylborohydrides currently known reduce camphor completely in 1 h or less at 0°. Presumably, the exceptionally slow reaction of camphor with LTSBH is an indication of the very large steric requirements of this reagent. This is a new development in trialkylborohydride chemistry and should find use in the regioselective reduction of a particular carbonyl group in a polycarbonyl substrate.[11]

The following procedure for the reduction of 4-*tert*-butylcyclohexanone is representative. An oven-dried 250-ml flask, equipped with a sidearm fitted with a Teflon stopcock, a magnetic stirring bar, and a reflux condenser, connected to a mercury bubbler, was cooled to room temperature under a dry stream of nitrogen. Lithium trisiamylborohydride solution in THF (67 ml, 28 mmol) was introduced into the reaction flask and cooled to −78° (dry ice-acetone). Then 3.7 g (24 mmol) of 4-*tert*-butylcyclohexanone, dissolved in 25 ml of THF (maintained at 0°), was added. The resulting mixture was stirred vigorously for 2 h at −78° and then allowed to equilibrate to room temperature (1 h). The reaction mixture was hydrolyzed with 4 ml of water and 15 ml of ethanol added; the organoborane was oxidized with 10 ml of 6 M sodium hydroxide and 15 ml of 30% hydrogen peroxide. The aqueous phase was saturated with anhydrous potassium carbonate, the organic phase separated, and the aqueous phase extracted with two 20-ml portions of Et_2O–THF. The combined extracts were dried ($MgSO_4$). GLC analysis of the extract indicated the presence of *cis*-4-*tert*-butylcyclohexanol, >99.5% isomerically pure. The volatile solvents and the siamyl alcohol were removed under reduced pressure to give 3.65 g (98%) of essentially pure *cis*-4-*tert*-butylcyclohexanol as a snow-white solid, mp 80° (lit.[12] mp 82°).

In conclusion, it should be pointed out that the discovery of these new hydride reagents has provided a convenient procedure for the conversion of unhindered ketones to the corresponding thermodynamically less stable alcohols in 99% or better isomeric purity. The unusual selectivity exhibited by these reagents arising from their very high steric requirements has major potential for selective reductions, and we are actively exploring this feature.[13]

References and Notes

(1) Siamyl is used as a convenient common name for the 3-methyl-2-butyl group.
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(5) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972.
(6) H. C. Brown, "Organic Synthesis via Boranes", Wiley, New York, N.Y., 1975.
(7) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 1491 (1971).
(8) (a) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 1241 (1961); (b) H. C. Brown and A. W. Moerikofer, *Ibid.*, **84**, 1478 (1962).
(9) Appearance of two pairs of doublets in ^{11}B instead of a single pair may be attributed to the presence of two diastereomeric forms of borohydrides in the ratio of 3:1.
(10) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, pp 84–132.
(11) Lithium dimesitylborohydride, a hindered diarylborohydride has been reported to reduce camphor very sluggishly, J. Hooz, S. Akiyama, F. J. Cedar, M. J. Bennett, and R. M. Tuggle, *J. Am. Chem. Soc.*, **96**, 274 (1974).
(12) E. L. Eliel, T. W. Doyle, R. O. Hutchins, and E. C. Gilbert, *Org. Synth.*, **50**, 13 (1970).
(13) Research underway with Dr. S. Krishnamurthy.
(14) Postdoctoral Research Associate on a Grant No. DA-ARO-D-31-124-73-G148, supported by the U.S. Army Research Office (Durham).

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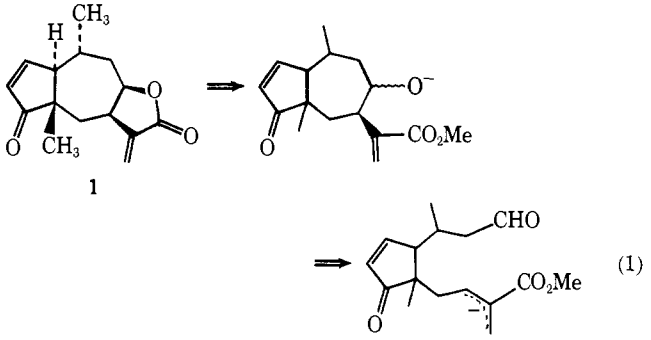
Synthetic Methods for Sesquiterpene α-Methylene-γ-lactones

Sir:

The naturally occurring sesquiterpene α-methylene-γ-lactones such as vernolepin and aromaticin (**1**) need no introduction as targets for organic synthesis.[1] This class of biolog-

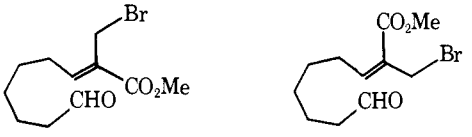
ically active compounds includes a variety of carbocyclic structures, often with the α-methylene-γ-lactone unit fused to six-,[2] seven-,[6] and ten-membered[8] carbocyclic rings. The α-methylene-γ-lactone unit has been assigned a central role in the mechanism of action of the many antitumor agents which bear this functional group,[10] and, because of its high reactivity, demands careful consideration in a synthetic strategy. Many methods are now available for introduction of the *exo*-methylene unit into a γ-lactone ring,[1] but a more direct strategy, and the mildest of reaction conditions, would seem advantageous when considering the complex functional groups often present in the natural α-methylene-γ-lactones.

We wish to report preliminary results concerning an approach to this structural type which involves simultaneous construction of a carbocyclic ring and the fused α-methylene-γ-lactone under particularly mild conditions, following the strategy outlined in eq 1 using aromaticin (**1**) as target.



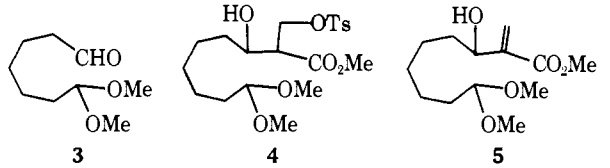
1 (1)

Because of the frequency of occurrence of perhydroazulene derivatives and their consistently high biological activity,[7] we have focused on a model system (**2**) which provides a seven-membered carbocyclic ring fused to an α-methylene-γ-lactone unit. Important questions include: (1) the efficiency and generality of methods which produce the α-bromomethylacrylate/aldehyde combination in precursor **2**, (2) choice of reagent for inducing the carbon-carbon ring closure, and (3) the stereochemistry of the ring fusion after (spontaneous) lactonization.



2a **2b**

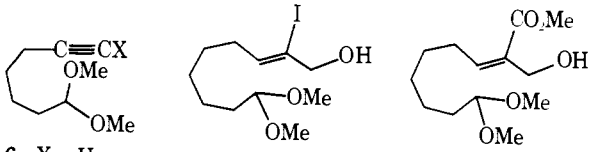
The *Z* isomer (**2a**) of the model was obtained in 43% yield overall from 7,7-dimethoxyheptanal (**3**).[11] Treatment of **3** with the dilithium salt of methyl 2-hydroxypropionate[12] followed by *p*-toluenesulfonyl chloride (1 mol equiv) produces the sulfonate ester **4** in 63% yield. Then elimination of *p*-toluenesulfonic acid (promoted by diazabicyclo[5.4.0]undec-5-ene, 0°, ether) afforded the allylic alcohol, **5** (90% yield after column chromatography). Reaction of **5** with phosphorus tribromide (0°, ether) proceeded with stereospecific allylic rearrangement to the *Z* configuration of the double bond and spontaneous unmasking of the acetal unit to produce **2a** in yields of 81-87%. The configuration of the double bond in **2a** is most strongly indicated by a triplet (1 H, J = 7.5 Hz) in the ^{1}H NMR spectrum at δ 6.96, characteristic of the syn-β-proton in acrylate esters;[13] high sensitivity FT ^{1}H NMR failed to detect



3 **4** **5**

absorption at δ 6.20 expected for the corresponding proton in the *E* isomer, **2b.** Brominations with allylic rearrangement usually give mixtures of isomeric olefins,[14] although a recent example of chlorination of a system related to **4** involves stereospecific rearrangement.[15]

The corresponding *E* isomer, **2b,** was obtained stereospecifically but in low overall yield following the method of Corey.[16] Reaction of lithium acetylide with the methanesulfonate ester of 6,6-dimethoxy-1-hexanol[17] produced the terminal alkyne, **6**. The acetylide anion from **6** was quenched with formaldehyde to generate the allylic alcohol **7**; then reduction of the lithium alkoxide (**8**) with diisobutylaluminum hydride followed by addition of iodine gave the *Z*-vinyl iodide, **9** (38% yield from **7**). Reaction of **9** with the combination sodium methoxide/nickel carbonyl produced the ester **10** (57%) uncontaminated by the geometrical isomer. Bromination with phosphorus tribromide (including unmasking of the aldehyde) afforded the *E*-bromoaldehyde **2b** in 61% yield. The characteristic triplet (1 H, J = 8.0 Hz) at δ 6.22 in the ^{1}H NMR spectrum confirmed the assignment of configuration; none of the *Z* isomer could be detected.



6, X = H
7, X = CH_2OH
8, X = CH_2OLi

9 **10**

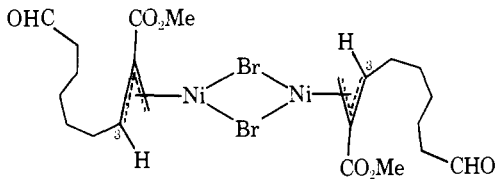
Reaction of *Z*-bromoaldehyde **2a** with zinc dust at 65° or zinc/copper couple[19] at 25° in tetrahydrofuran was complete in ca. 10 h.[20] Optimum yields of the α-methylene-γ-lactone **11a** were obtained using dilute solution, ca. 0.02 M in **2a.** Under these conditions, the lactone was obtained in a high state of purity (TLC, ^{1}H NMR, ir analysis) in 60-62% yield after isolation by preparative layer chromatography.[21] The purified product and the crude product showed no evidence of the corresponding trans-fused isomer **11b;** the characteristic ^{1}H NMR absorptions of the exocyclic methylene unit in **11b** were clearly absent.[22] Changes in the solvent (toluene, *N,N*-dimethylformamide) and higher dilution led to slower and less efficient reaction.

The isomeric allylic bromide, **2b,** was transformed under the same conditions (Zn-Cu couple, THF, 25°, 10 h) into a mixture of the cis-fused isomer (**11a,** 46% yield) and the trans-fused isomer (**11b,** 12% yield). The isomers were separated by preparative layer chromatography and conclusively identified by comparison of ^{1}H NMR spectra with data from material prepared by a different route.[22]

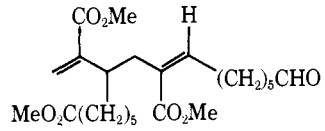
11a **11b**

Reaction of bis(1,5-cyclooctadiene)nickel[23] with the *Z*-bromoaldehyde **2a** in tetrahydrofuran at −17° for 3 h produced a red solution, presumably a π-allylnickel bromide dimer (**12** or an isomer at C-3).[24] After the mixture was stirred at 25° for 18 h, the cis-fused lactone, **11a,** was isolated by preparative layer chromatography in 52% yield. The trans-fused lactone **11b** was not detected, but a coupling product of the allylic bromide, tentatively identified as **13** by ^{1}H NMR and mass spectrometry, was isolated (15% yield). Under the same conditions, the *E*-bromoaldehyde **2b** produced the cis-fused lactone **11a** as the only isolated product (51% yield).[25]

Thus both metal reagents convert the bromoaldehydes (**2**) into the fused-ring α-methylene-γ-lactone structure (**11**) with a strong preference for cis ring fusion from both the *Z* and *E*



12



13

isomers of **2**. The consistent formation **11a** from both **2a** and **2b** suggests a common allyl-zinc intermediate and a common π-allylnickel intermediate (perhaps **12**);[25] this stereoselectivity also allows confidence that the model studies can be applied to total synthesis of natural products which bear the α-methylene-γ-lactone unit fused to a perhydroazulene skeleton in the cis geometry.[6,26]

References and Notes

(1) Cf. P. A. Grieco, *Synthesis*, 67 (1975).
(2) Examples of recent interest include vernolepin[3,4] and isotelekin.[5]
(3) S. M. Kupchan, R. J. Hemingway, D. Werner, A. Karim, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, **90**, 3596 (1968).
(4) Cf. P. A. Grieco, J. Noguez, and Y. Masahi, *Tetrahedron Lett.*, 4213 (1975), and references therein.
(5) R. B. Miller and E. S. Behare, *J. Am. Chem. Soc.*, **96**, 8102 (1974).
(6) Natural products with the α-methylene-γ-lactone fused to a seven-membered carbocyclic ring include a variety of perhydroazulene derivatives. For a few examples including biological testing results, see ref 1 and 7. For a more complete listing of more than 30 examples, see T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds", Vol II (Terpenes), Academic Press, New York, N.Y., 1972.
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(8) Complex structures containing ten-membered carbocyclic rings such as elephantopin[9] have potent biological activity,[7] and have not yet been successfully synthesized.
(9) S. M. Kupchan, Y. Aynehchi, J. M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *J. Am. Chem. Soc.*, **88**, 3674 (1966).
(10) Cf. S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. J. Giacobbe, *Science*, **168**, 376 (1970).
(11) Prepared from cycloheptanone in 65% yield overall via ozonolysis of 1-acetoxycycloheptene to give methyl 7,7-dimethoxyheptanoate. Then hydride reduction followed by selective oxidation (CrO_3/pyridine) produced 7,7-dimethoxyheptanal (**3**).
(12) J. L. Herrmann and R. H. Schlessinger, *Tetrahedron Lett.*, 2429 (1973).
(13) Cf. A. Löffler, R. J. Pratt, H. P. Rüesch, and A. S. Drieding, *Helv. Chim. Acta*, **53**, 383 (1970).
(14) For discussions, see (a) D. J. Faulkner, *Synthesis*, 175 (1971); (b) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, **90**, 2882 (1968).
(15) J. C. Depezay and Y. L. Merrer, *Tetrahedron Let.*, 2751, 2755 (1974).
(16) E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **92**, 6314 (1970).
(17) This compound was prepared by hydride reduction of methyl 6,6-dimethoxyhexanoate[18] which, in turn, was obtained from ozonolysis of 1-acetoxycyclohexene; the overall yield from cyclohexanone was 88%.
(18) C. D. Hard and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **74**, 5324 (1952)
(19) Prepared according to R. M. Blankenship, K. A. Burdett, and J. S. Swenton, *J. Org. Chem.*, **39**, 2300 (1974).
(20) A few examples of intramolecular Reformatsky-type reactions are known, but none involving formation of homoallylic alcohols. Cf. Table V in M. W. Rathke, *Org. React.*, **22**, 423 (1975).
(21) Intermolecular examples of reactions closely related to the conversion **2** → **11** have been reported: E. Ohler, K. Reininger, and U. Schmidt, *Angew. Chem., Int. Ed. Engl.*, **9**, 457 (1970).
(22) Comparisons were made directly with spectra of **11a** and **11b** kindly provided by Professor J. A. Marshall. Comparisons of chemical shift data with those quoted in the literature can be misleading; the absorptions due to the exocyclic methylene unit in the ^1H NMR spectra show substantial solvent (CCl_4 vs. $CDCl_3$) and concentration effects. The most reliable distinguishing features of the ^1H NMR spectra are the shapes of the envelopes in the region δ 1.8–3 due to the aliphatic $-CH_2-$ units.
(23) For convenient preparations, see (a) M. F. Semmelhack, *Org. React.*, **19**, 178 (1972); (b) R. A. Schunn, *Inorg. Synth.*, **13**, 124 (1973).
(24) The reaction of allylic halides with bis(1,5-cyclooctadiene)nickel is a general, mild method for formation of π-allylnickel halide complexes: G. Wilke et al., *Angew. Chem., Int. Ed. Engl.*, **5**, 151 (1966).
(25) The reaction of π-allylnickel halide complexes with aldehydes has been reported: (a) E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.*, **89**, 2755 (1967); (b) L. S. Hegedus, S. D. Wagner, E. L. Waterman, and K. Siirala-Hansen, *J. Org. Chem.*, **40**, 593 (1975). The latter reference includes intermolecular examples closely related to the conversion **2** → **11** using zerovalent nickel reagents.
(26) We are grateful to the National Institutes of Health for generous financial support (Grant AI-08687).
(27) Recipient of a Camille and Henry Dreyfuss Teacher-Scholar Award, 1973–1978.

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On the Entropic Control of Chemiluminescent Reactions

Sir:

Perrin has discussed the efficiency of chemiluminescent reactions from a thermodynamic point of view and concluded that in some systems there must be a "thermodynamic control" which puts a limit to the emission quantum yield.[1] This conclusion was based on the analysis of a cycle that would otherwise transform heat into work, violating the second principle. We consider that the proposed cycle really shows that a chemiluminescent reaction cannot be employed to transform heat into work and not that the reaction cannot take place with a high quantum yield. Let us consider the cycle proposed by Perrin[1]

Step i: The chemiluminescent reaction

$$A \rightarrow B + h\nu \tag{1}$$

takes place isothermally at a temperature T.

Step ii: The radiation emitted in step i enters a Carnot machine that produces an amount of work W_{max} and converts some of the energy into heat (which goes to a reservoir at temperature T); and

Step iii: Work is employed to regenerate A in the reaction

$$B \rightarrow A$$

which also takes place at temperature T.

If we define

$$\Delta G = \bar{G}_B - \bar{G}_A$$

the second principle requires that, for the first step

$$-\Delta G \geq N_{Av}h\nu - TS_R \tag{2}$$

where S_R is the entropy associated with the radiation.[2]

For the machine, the maximum work obtainable is given by

$$W_{max} = N_{Av}h\nu(T_e - T)/T_e \tag{3}$$

where T_e is the temperature associated to the radiation.[2] If we consider that

$$S_R = N_{Av}h\nu/T_e \tag{4}$$

from eq 2 and 3 we obtain that

$$W_{max} \leq -\Delta G \tag{5}$$

This last equation shows that the maximum work obtainable is always less (or equal if all the processes were reversible) than the work required by step iii, even if the quantum yield of the chemiluminescent reaction is 1. Work must then be expended in running any real machine comprising this cycle. We can conclude then that, thermodynamics does not impose any control on the quantum yield of a chemiluminescent reaction. Thermodynamics, through eq 2, can determine if reaction 1 or reaction 6

$$B + h\nu \rightarrow A \tag{6}$$

is faster under a given set of experimental conditions (concentrations, temperature and density of the radiation field),