Table I. Products of the Directed Aldol Reaction of Lithium Enolate of Ethyl Fluoroacetate

$LiCHFCO_2CH_2CH_3 + RR'CO \rightarrow RR'COHCHFCO_2CH_2CH_3$

	R	R′	yield, %	diastereoselectivity
1	CH_3	$(CH_3)_3C$	95	1:3.8[a]
2	CH_3	CH_2CH_3	82	1:1
3	CH_3	Ph	96	1:1.6[a]
4	CH_3	C_5H_{11}	93	1:1.1[a]
5	Ph	Ph	70	
6	2-adamantyl		75	
7	2-norbornyl		91	
8	H	$(CH_3)_3C$	85	1:3
9	H	C_6H_{13}	20	1:2
10	H	Ph	93	1:2
11	H	3,3-dimethyl-2,4-dioxol-1-yl	55	1:1.2

[a] Syn to anti.

above 50 °C. The relative ratio of *E*:*Z* enol ether differs significantly from the 95:5 ratio formed by enolization and trapping of methyl propionate under similar conditions.[12]

The relative configuration of the aldol adducts was determined by ^{13}C NMR spectroscopy employing the observations of Heathcock.[13] Fluorohydrins may be expected to exhibit a highly favored conformational preference for hydrogen bonding between fluorine and hydroxylic proton (Scheme I). Energy of the stabilization of the favored conformation has been determined to be as much as 2 kcal/mol in fluoroethanol.[14] Gauche interactions of the methyl group from methyl ketone coupling partners and the ester function of the enolate component result from this strong conformational preference. When products having the syn[15] configuration are formed, this gauche interaction may be predicted to result in an upfield shift of the methyl resonance in the ^{13}C NMR spectrum. The determination of the configuration of the major product of reaction with pinacolone as anti is in agreement with the product stereochemistry predicted for the reaction of an *E* enolate with the ketone if the Zimmerman chair-preferred transition state is applied (Scheme II). The failure to observe better diastereoselection is in agreement with our failure to observe selectivity in enolate formation. Extension of this method to aldehyde condensation products by correlation of the chemical shift of the carbon bearing fluorine and the carbinol carbon with the assignments determined for methyl ketones is not possible because no consistent chemical shift trend is observed.[13]

Single-crystal X-ray diffraction studies of the products, as well as the synthesis of appropriate derivatives of the products, are in progress to confirm relative stereochemical assignments made by NMR. Additional experiments to confirm that kinetic stereoselectivity is important in controlling product formation are also under way. The synthesis of fluorinated biologically active materials using these methods will be reported shortly.

Experimental Section

Ethyl fluoroacetate (Sigma)[6] was used without further purification. Aldehydes and ketones were purified by fractional distillation from calcium sulfate. THF was purified by distillation from sodium benzophenone ketyl. Hexamethyldisilazane and HMPA were purified by distillation from calcium hydride. Infrared spectra were recorded on a Perkin-Elmer Model 283 or 710B infrared spectrometer. ^1H magnetic resonance spectra were determined on a Varian EM-360A and a Bruker WH 90D spectrometer. ^{13}C magnetic resonance spectra were measured on a Bruker WH 90D. Analytical samples were prepared by preparative thin-layer chromatography on silica gel $F_{254,366}$ (E. Merck). Combustion analyses were performed by Galbraith Laboratories (Knoxville, TN).

Typical Procedure for Enolate Formation and Aldol Reaction. To a stirred round-bottomed flask containing 50 mL of anhydrous THF and 6.1 mL (0.03 mol) of hexamethyldisilazane was added 20 mL (0.03 mol) of a 1.5 M solution of methyllithium in diethyl ether. After methane evolution ceased the temperature was lowered to −85 °C, and 1.79 g (0.010 mol) of HMPA and 0.97 mL (0.010 mol) of ethyl fluoroacetate were added dropwise as rapidly as possible while not allowing the temperature to rise above −85 °C. After 5 additional min 0.005–0.01 mol of the carbonyl compound was added quickly. The mixture was allowed to stir 10 additional min and then was quenched at −85 °C with 5 mL of saturated ammonium chloride. On warming to room temperature the mixture was diluted with 60 mL of distilled hexanes. Separation followed by washing with four 100-mL portions of water, drying over anhydrous magnesium sulfate, and evaporation of the solvent in vacuo yielded the crude product.

Acknowledgment. We thank the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. $CH_2FC(O)OEt$, 459-72-3; $LiCHFC(O)OEt$, 83192-17-0; (*E*)-$CHF{=}C(OEt)OSiMe_3$, 92397-82-5; (*Z*)-$CHF{=}C(OEt)OSiMe_3$, 92397-83-6; (*R**,*R**)-*t*-$BuC(CH_3)(OH)CHFC(O)OEt$, 92397-84-7; (*R**,*S**)-*t*-$BuC(CH_3)(OH)CHFC(O)OEt$, 92397-85-8; (*R**,*R**)-$CH_3CH_2C(CH_3)(OH)CHFC(O)OEt$, 92397-86-9; (*R**,*S**)-$CH_3CH_2C(CH_3)(OH)CHFC(O)OEt$, 92397-87-0; (*R**,*R**)-$PhC(CH_3)(OH)CHFC(O)OEt$, 92397-88-1; (*R**,*S**)-$PhC(CH_3)(OH)CHFC(O)OEt$, 92397-89-2; (*R**,*R**)-$CH_3(CH_2)_4C(CH_3)(OH)CHFC(O)OEt$, 92397-90-5; (*R**,*S**)-$CH_3(CH_2)_4C(CH_3)(OH)CHFC(O)OEt$, 92397-91-6; $Ph_2C(OH)CHFC(O)OEt$, 427-31-6; (*R**,*R**)-*t*-$BuCH(OH)CHFC(O)OEt$, 92397-94-9; (*R**,*S**)-*t*-$BuCH(OH)CHFC(O)OEt$, 92397-95-0; (*R**,*R**)-$CH_3(CH_2)_5CH(OH)CHFC(O)OEt$, 92397-96-1; (*R**,*S*,*)-$CH_3(CH_2)_5CH(OH)CHFC(O)OEt$, 92397-97-2; (*R**,*R**)-$PhCH(OH)CHFC(O)OEt$, 50778-15-9; (*R**,*S**)-$PhCH(OH)CHFC(O)OEt$, 50778-16-0; $CH_3C(O)C(CH_3)_3$, 75-97-8; $CH_3C(O)CH_2CH_3$, 78-93-3; $CH_3C(O)Ph$, 98-86-2; $CH_3C(O)(CH_2)_4CH_3$, 110-43-0; $PhC(O)Ph$, 119-61-9; $(CH_3)_3CCHO$, 630-19-3; $CH_3(CH_2)_5CHO$, 111-71-7; PhCHO, 100-52-7; ethyl 2-hydroxy-α-fluoro-2-adamantaneacetate, 92397-92-7; ethyl 2-methyl-α-fluoro-2-norbornaneacetate, 92397-93-8; 2-adamantanone, 700-58-3; 2-norbornanone, 497-38-1.

Supplementary Material Available: Complete spectral and analytical data for all new compounds (4 pages). Ordering information is given on any current masthead page.

(12) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1979**, *45*, 1066–1081.
(13) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294–4299.
(14) (a) Buckley, P.; Giguere, P. A.; Yamamoto, D. *Can. J. Chem.* **1968**, *46*, 2917–2923. (b) Krueger, P. J.; Mettee, H. D. *Can. J. Chem.* **1964**, *42*, 326–339.
(15) When the main chain of the molecule is drawn in a zig–zag fashion and the two substituents, fluorine and hydroxyl, are on the same side of plane defined by the main chain, the molecule has been described as having a syn relationship. When fluorine and hydroxyl lie on opposite sides of this plane, the relationship has been denoted as anti.

Complexation of *ent*-8,13β-Epoxylabdane-12,14-diols with Boric Acid. A Method for Establishing the C(14) Configuration[1]

Francisco Fernández-Gadea and Benjamín Rodríguez*

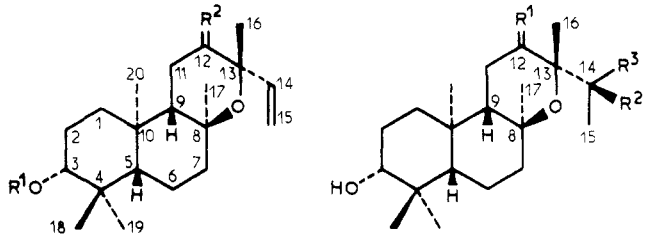
Instituto de Química Orgánica, CSIC, Juan de la Cierva 3, Madrid-6, Spain

Received May 23, 1984

Among natural substances of the diterpene type there exist some compounds containing a vicinal glycol unit in

0022-3263/84/1949-4721$01.50/0

Chart I



	R^1	R^2
1	H	
2	Ac	
5	Ac	O
6	H	
7	Ac	

	R^1	R^2	R^3
3		H	OH
4		OH	H
8		H	OH
9		OH	H

the form of a 13-dihydroxyethyl group.[2,3] The configuration of their secondary hydroxy group of the dihydroxyethyl moiety has remained obscure in some cases because of the nonrigid nature of the C(13)-attached side chain. Recently interest has been focused on ^{13}C NMR spectroscopy as a tool for the determination of C(15) configurations in pimarene-, isopimarene-, and sandaracopimarene-15,16-diols by means of a ^{13}C NMR spectral analysis of their cyclization products.[2] Moreover, we have recently reported[3] some simpler and better criteria for establishing the C(13) and C(14) configurations of 8,13- and 8,13β-epoxylabdane-14,15-diols by comparing the ^{13}C NMR spectrum of the C(14),C(15)-dihydroxy compound with that of its 14,15-diacetyl or 14,15-acetonide derivative[3a] and also by application of boric acid induced ^{13}C NMR shifts on each pair of the C(14) epimers.[3b,c] The determination of the C(14) configuration of either *ent*-8,13β-epoxylabdane-3β,12α,14- or -3β,12β,14-triols by a ^{13}C NMR spectroscopic analysis of their C(12),C(14)-borate anion cyclic complexes is the subject of the present paper.

The natural diterpenoid varodiol[4] [*ent*-8,13β-epoxylabd-14-ene-3β,12α-diol (**1**), Chart I] was used as the starting material for obtaining all the products (**2**–**9**). Treatment of varodiol diacetate (compound **2**) with *m*-chloroperbenzoic acid in the presence of 2,6-di-*tert*-butyl-4-methylphenol as a radical inhibitor[5] yielded a mixture of the C(14),C(15)-epoxy derivatives epimeric at C(14). This mixture was reduced with $LiAlH_4$ to give compounds **3** and **4** which were easily separated on column chromatography. Reduction with $LiAlH_4$ of the derivative **5**[4] quantitatively yielded 12-epivarodiol (**6**), the diacetate of which (compound **7**) was transformed into compounds **8** and **9** as described above for their C(12) epimers (compounds **3** and **4**, respectively).

Table I. ^{13}C Chemical Shifts and Boric Acid Shifts of Compounds 3, 4, 8, and 9[a]

	3		4		8		9	
	δ	$\Delta\delta^b$	δ	$\Delta\delta^b$	δ	$\Delta\delta^b$	δ	$\Delta\delta^b$
C(1) t	37.5	−0.2	37.4	−0.1	37.9	−0.3	37.9	−0.2
C(2) t	27.6	−0.2	27.6	−0.2	27.7	−0.3	27.8	−0.2
C(3) d	78.0	0.0	78.0	0.0	78.0	0.0	78.0	0.0
C(4) s	39.1	−0.1	39.1	−0.1	39.2	−0.1	39.2	−0.1
C(5) d	55.7	0.0	55.7	0.0	55.5	0.7	55.4	−0.1
C(6) t	20.1	0.0	20.1	−0.1	20.1	0.3	20.1	−0.2
C(7) t	44.1	0.0	44.1	0.0	43.8	1.2	43.4	−0.3
C(8) s	74.7	1.2	74.3	1.2	75.4	−4.8	75.5	−1.0
C(9) d	51.4	0.3	51.5	0.2	56.8	−6.1	57.7	−0.9
C(10) s	36.9	0.4	36.9	0.4	36.7	0.4	36.7	−0.1
C(11) t	25.5	−2.0	25.3	−1.9	26.7	−1.4	25.8	−0.6
C(12) d	64.9	−0.6	70.3	1.5	77.5	−2.4	80.5	−0.8
C(13) s	78.4	−6.0	76.8	−5.0	79.4	−5.0	77.7	−1.9
C(14) d	71.3	5.6	76.1	2.6	70.0	2.2	69.1	−1.1
C(15) q	17.9	0.4	17.1	−1.7	19.1	−3.7	18.2	−2.1
C(16) q	20.7	2.2	17.6	−2.0	25.5	−0.8	22.7	−1.1
C(17) q	26.2	0.8	26.7	0.7	23.5	1.2	24.0	0.5
C(18) q	28.4	0.0	28.4	0.0	28.3	0.0	28.4	−0.1
C(19) q	15.9	0.0	15.9	0.0	15.7	0.1	15.8	−0.1
C(20) q	15.1	−0.2	14.9	−0.2	16.3	−1.3	16.4	−0.1

[a] In parts per million downfield from Me_4Si. In $CDCl_3$–pyridine-d_5 (1:1) solution. [b] After saturation with H_3BO_3.[3b,7]

The 14*R* configurations of compounds **3** and **8**, as well as the 14*S* configuration of their C(14) epimers (compounds **4** and **9**, respectively), were established by application of Horeau's method of partial resolution[6] to compounds **1**, **3**, and **4**, and **6**, **8**, and **9**, which defined as 14*R* the absolute configuration of the triols **3** and **8** and as 14*S* the absolute configuration at C(14) in compounds **4** and **9** (see also the Experimental Section).

The ^{13}C NMR spectra of compounds **3**, **4**, **8**, and **9** were obtained in $CDCl_3$–C_5D_5N (1:1, v/v) solution before and after addition of boric acid.[3b,c,7] The ^{13}C shifts and boric acid shifts of these compounds are listed in Table I and were assigned on the basis of ^{13}C NMR off-resonance-decoupled spectra, comparison of pairs of compounds, general chemical shift arguments, and literature data on closely related structures.[3a,b,4,8]

The data collected in Table I show that the C(14) epimers (pairs of compounds: **3**,**4**; **8**,**9**) are distinguished by their C(12) and C(16) shifts, since the γ effects of the C(14)-hydroxyl group on C(12) and C(16) are different in each epimer. In the case of the 14*R* derivatives (**3** and **8**) C(12) appear at higher field than in their 14*S* epimers (**4** and **9**, respectively), whereas the C(16) carbon atom of compounds **3** and **8** (14*R* configuration) are shifted downfield with respect to those of the corresponding 14*S* epimers (**4** and **9**, respectively).

The differences in the C(12) and C(16) chemical shifts of these substances arise from intramolecularly hydrogen bonded forms between the C(14)-hydroxyl group and the C(8),C(13)-ether functions[3b] or/and the C(12) secondary alcohols, which cause preferred rotamers of the side chain of these diterpenoids.

Since we were interested in finding a simple method which would allow an unambiguous determination of the configuration at C(14), we considered that the ^{13}C NMR differences between these substances should be maximized

(1) Dedicated to Professor Dr. Manuel Lora-Tamayo, Complutense University of Madrid, Spain, on the occasion of his 80th birthday.

(2) (a) Wenkert, E.; Ceccherelli, P.; Raju, M. S.; Polonsky, J.; Tingoli, M. *J. Org. Chem.* **1979**, *44*, 146 and references therein. (b) Wenkert, E.; Raju, M. S.; Ceccherelli, P.; Curini, M.; Tingoli, M.; Pellicciari, R. *J. Org. Chem.* **1980**, *45*, 741. (c) Wenkert, E.; Halls, T. D. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1981**, *46*, 3135.

(3) (a) García-Alvarez, M. C.; Rodríguez, B. *J. Org. Chem.* **1981**, *46*, 1915. (b) García-Alvarez, M. C.; Rodríguez, B.; García-Granados, A.; de Buruaga, A. S. *J. Org. Chem.* **1982**, *47*, 3571 and references therein. (c) García-Alvarez, M. C.; Rodríguez, B. *An. Quim. Ser. C* **1982**, *78*, 371.

(4) Algarra, J.; García-Granados, A.; de Buruaga, A. S.; de Buruaga, J. M. S. *Phytochemistry* **1983**, *22*, 1779.

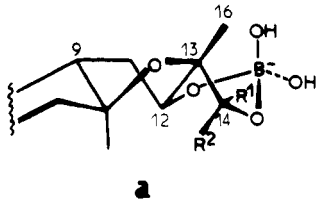
(5) Khisi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

(6) Horeau, A.; Nouaille, A. *Tetrahedron Lett.* **1971**, 1939.

(7) Fernández-Gadea, F.; Jimeno, M. L.; Rodríguez, B. *Org. Magn. Reson.* **1984**, *22*, 515.

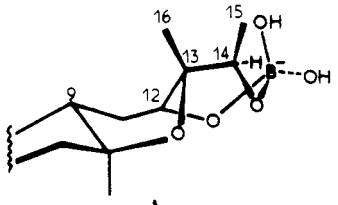
(8) (a) Wahlberg, I.; Karlsson, K.; Nishida, T.; Cheng, K.-P.; Enzell, C. R.; Berg, J.-E.; Pilotti, A.-M. *Acta Chem. Scand., Ser. B* **1977**, *31B*, 453. (b) Wahlberg, I.; Curvall, M.; Enzell, C. R. *Acta Chem. Scand., Ser. B* **1978**, *32B*, 310.

Chart II

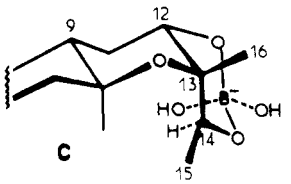


a

	R^1	R^2
3	H	Me
4	Me	H



b



c

if the rotation of their side chain is completely restricted. Consequently, we fixed the conformation of the side chain of these diterpenoids by means of the formation of a cyclic borate complex between the C(12)- and C(14)-hydroxyl groups.[3b,c,7] Table I shows that the formation of these complexes produced substantial modifications in the ^{13}C NMR shifts of compounds **3**, **4**, **8**, and **9**. These effects can be used for establishing the C(14) configuration in each substance,[3b,c] even when only one of the epimers is available. Thus, in compound **3** [(14*R*)-*ent*-12α,14-dihydroxy derivative] the formation of the borate complex causes, besides the expected shifts[3b,c,7] of C(11), C(13), C(14), and C(15), an upfield shift of C(12) ($\Delta\delta$ = −0.6) and a downfield shift of C(16) ($\Delta\delta$ = 2.2), whereas in its C(14) epimer (compound **4**) complexation with boric acid causes a downfield shift of C(12) ($\Delta\delta$ = 1.5) and an upfield shift of C(16) ($\Delta\delta$ = −2.0). In the case of the *ent*-12β-hydroxy derivatives (compounds **8** and **9**) addition of boric acid causes upfield shifts of C(12) and C(16) in both C(14) epimers (Table I). However, complexation of compound **8** (14*R* epimer) causes large upfield shifts of C(8), C(9), and C(20) ($\Delta\delta$ = −4.8, −6.1, −1.3, respectively) and downfield shifts of C(5), C(7), and C(14) ($\Delta\delta$ = 0.7, 1.2, 2.2, respectively), which are clearly different from those observed in the 14*S* epimer (compound **9**, see Table I). The complexation of boric acid with compound **8** causes a drastic conformational change in the ring C of this substance, a change that does not occur for the 14*S* epimer (**9**).[3b]

Thus, from the above data it is clear that the C(14) configurations of these compounds (**3**, **4**, **8**, and **9**) can be firmly established by comparing their ^{13}C NMR spectra with those obtained after complexation with boric acid.

Inspection of Dreiding molecular models of the borate complexes of the four compounds (**3**, **4**, **8**, and **9**), together with the observed $\delta_{C(12)}$ and $\delta_{C(16)}$ values (Table I) and the simple consideration that the shielding magnitude of the γ-gauche effect is greater than the γ-trans effect, allowed the assignment of a specific ring-C conformation for each compound. Each borate complex possesses, probably, the following ring-C conformation. Compounds **3** and **4**, both a $B_{8,12}$ conformation (**a**, Chart II) in which the C(14)-oxygenated substituent and the ethereal oxygen atom of ring C are antiperiplanar; compound **8**, a $^{9,13}B$ conformation (**b**) in which the C(14)-hydrogen and the ethereal oxygen atoms are antiperiplanar; and compound **9**, a $^{12}C_8$ conformation (**c**) with an antiperiplanar configuration between the C(14)-oxygenated substituent and the oxygen atom of the ether bridge. In particular, the $\delta_{C(12)}$ and $\delta_{C(16)}$ values of the borate complex of compounds **3** (δ 64.3 and 22.9, respectively) and **4** (δ 71.8 and 15.6, respectively) are in agreement with the above conclusions, because in compound **3** the C(12) carbon atom is γ-gauche oriented with respect to both Me-15 and C(14)-oxygenated functions (two γ-gauche effects), whereas in compound **4** it is γ-trans with respect to Me-15 and γ-gauche with respect to the C(14)-oxygen atom, thus, appearing at higher field in **3** ($\delta_{C(12)}$ 64.3) than in **4** ($\delta_{C(12)}$ 71.8). A similar reasoning also explains the behavior of C(16) in these compounds. Furthermore, the $\delta_{C(9)}$ values of compounds **3**, **4**, **8**, and **9**, and those of the corresponding borate complexes (Table I), clearly revealed that in **3** and **4** the ring-C conformation is the same in both compounds ($\delta_{C(9)}$ 51.4 and 51.5, respectively) and also it is the same in their borate complexes ($\delta_{C(9)}$ 51.7 in both substances), whereas the ring-C conformation of compounds **8** and **9** is also the same ($\delta_{C(9)}$ 56.8 and 57.7, respectively), but it changes in the borate complex of compound **8** ($\delta_{C(9)}$ at 50.7 in **8**, and at 56.6 in **9**). Moreover, these data also establish that the conformation of the ring C of compounds **3** and **4** is not the same that in compounds **8** and **9**.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter with a 1-dm cell. Elemental analyses were carried out in our Institute on a Perkin-Elmer 240 analyzer. IR spectra were obtained with a Perkin-Elmer 681 spectrometer, and mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6MG instrument. ^1H NMR spectra (pyridine-d_5) were measured at 90 MHz on a Varian EM-390 spectrometer, with Me_4Si as an internal standard. ^{13}C NMR spectra were obtained on a Bruker WP-80 spectrometer at a frequency of 20.15 MHz. All samples were prepared as 0.5 M $CDCl_3$–pyridine-d_5 (1:1, v/v) solutions in 5-mm sample tubes. The probe temperature in each case was 36 °C. Chemical shifts are in ppm downfield from internal Me_4Si and are considered to be accurate to ±0.05 ppm. To observe H_3BO_3-induced shifts, pure boric acid was added in small amounts to the $CDCl_3$–C_5D_5N solution of the sample tube until a thin layer of H_3BO_3 ($\simeq$2-mm high) appeared in the bottom after stirring (saturated solution). The substrate sample was easily recovered by addition of 0.1 N HCl solution and extraction with $CHCl_3$.

Compounds **1**, **2**, and **5** have been previously described.[4]

(14*R*)-*ent*-8,13β-Epoxylabdane-3β,12α,14-triol (3) and (14*S*)-*ent*-8,13β-Epoxylabdane-3β,12α,14-triol (4) from Varodiol Diacetate (2). To a CH_2Cl_2 (50 mL) solution of compound **2**[4] (410 mg) were added 359 mg of *m*-chloroperbenzoic acid (MCPBA) and 25 mg of 2,6-di-*tert*-butyl-4-methylphenol (DTHT),[5] and the solution was refluxed for 5 h. Workup in the usual manner yielded a mixture of the (14*R*)- and (14*S*)-14,15-epoxy derivatives of varodiol diacetate in addition to starting material (**2**). This mixture was chromatographed on a silica gel (400 g, Merck No. 7734 deactivated with 15% H_2O) dry column; elution with *n*-hexane–EtOAc (9:1) yielded compound **2** (80 mg) and a mixture of the two C(14) epimeric 14,15-epoxy derivatives (230 mg). This mixture was treated in an Et_2O (30 mL) solution with $LiAlH_4$ (600 mg) for 3 h under reflux. The products (**3** and **4**) of this reaction were chromatographed on a silica gel column eluted with $CHCl_3$–MeOH (49:1) to give pure **3** (60 mg) followed by **4** (75 mg).

3: mp 99–103 °C (from EtOAc–*n*-hexane); $[\alpha]^{20}_D$ −20.1° (*c* 0.36, MeOH); IR (KBr) 3420, (br, OH), 3000, 2950, 2880, 1455, 1390, 1380, 1050, 1045, 990 cm^{-1}; ^1H NMR δ 4.10 (2 H, complex, H-12 and H-14), 3.30 (1 H, dd, $J_{aa'}$ = 9 Hz, $J_{ae'}$ = 6 Hz, H-3), 1.33 (3 H, d, J = 6 Hz, 3 H-15), CMe singlets at 1.45, 1.27, 1.10, 0.93, and 0.80; mass spectrum (EI, 75 eV, direct inlet), *m/z* (relative intensity) M^+ absent, 325 (M^+ − 15, 3), 295 (100), 277 (90), 259 (60), 207 (75), 190 (55), 189 (40), 175 (40), 149 (75), 123 (35), 121 (40),

109 (35), 95 (40), 81 (50), 71 (35), 69 (50). Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.27; H, 10.48.

4: an amorphous solid, mp 110–119 °C; $[\alpha]^{20}_D$ −25.9° (*c* 0.35, MeOH); IR (KBr) 3420 (br, OH), 2950, 2880, 1455, 1390, 1380, 1040, 1030, 990 cm^{-1}; ^{1}H NMR δ 4.57 (1 H, m, $W_{1/2}$ = 9 Hz, H-12), 4.10 (1 H, q, J = 6 Hz, H-14), 3.36 (1 H, dd, $J_{aa'}$ = 9 Hz, $J_{ae'}$ = 6 Hz, H-3), 1.48 (3 H, d, J = 6 Hz, 3H-15), CMe singlets at 1.53, 1.19, 1.11, 0.96, and 0.79. Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.26; H, 10.31.

Application of Horeau's Method to Compounds 1, 3, and 4. This was performed in the usual manner.[6] Compound **1** (24.67 mg, 0.0765 mmol) and (±)-α-phenylbutyric anhydride (APBA, 142.47 mg, 0.459 mmol) in pyridine solution (2.00 mL): $\alpha_1 - 1.1\alpha_2$ = +0.300 for the 3*R* and 12*R* centers. Compound **3** (26.00 mg, 0.0765 mmol) and APBA (142.47 mg, 0.459 mmol) in pyridine solution (2.00 mL): $\alpha_1 - 1.1\alpha_2$ = +0.414 for the 3*R*, 12*R*, and 14 centers; thus, 0.414 − 0.300 = +0.114 for the C(14)-hydroxyl group, configuration 14*R*. Compound **4** (26.00 mg, 0.0765 mmol) and APBA (142.47 mg, 0.459 mmol) in pyridine solution (2.00 mL): $\alpha_1 - 1.1\alpha_2$ = +0.171 for the 3*R*, 12*R*, and 14 centers; thus, 0.171 − 0.300 = −0.129 for the C(14)-hydroxyl group, configuration 14*S*. This experiment was performed with identical time reaction (17 h) and temperature (19 °C) for the three compounds.

(14*R*)-*ent*-8,13β-Epoxylabdane-3β,12β,14-triol (8) and (14*S*)-*ent*-8,13β-Epoxylabdane-3β,12β,14-triol (9) from Compound 5. The keto derivative **5**[4] (400 mg) was treated with $LiAlH_4$ in Et_2O solution at room temperature for 4 h, yielding 12-epivarodiol (**6**, 350 mg): mp 99–101 °C (EtOAc–*n*-hexane); $[\alpha]^{23}_D$ −48.7° (*c* 0.37, MeOH); IR (KBr) 3490, 3420, 3260 (hydroxyl groups), 3080, 1660, 920 (vinyl group), 2950, 2880, 1460, 1390, 1070, 1040 cm^{-1}; ^{1}H NMR δ 6.41 (1 H, dd, J_1 = 18 Hz, J_2 = 10 Hz, H-14), 5.47 (1 H, dd, J_1 = 18 Hz, J_2 = 1.8 Hz, H-15), 5.20 (1 H, dd, J_1 = 10 Hz, J_2 = 1.8 Hz, H'-15), 3.57 (1 H, dd, $J_{aa'}$ = 10 Hz, $J_{ae'}$ = 6 Hz, H-12), 3.21 (1 H, dd, $J_{aa'}$ = 9 Hz, $J_{ae'}$ = 6 Hz, H-3), CMe singlets at 1.39, 1.24, 1.00, and 0.76 (6 H); mass spectrum (EI, 75 eV, direct inlet), *m*/*z* (relative intensity) M$^+$ absent, 307 (M$^+$ − 15, 8), 279 (10), 208 (50), 190 (100), 175 (85), 147 (32), 121 (38), 101 (28), 81 (40), 71 (45), 69 (38). Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.36; H, 10.55. Compound **6** was transformed into its diacetyl derivative **7** in the usual manner, and this diacetate (**7**, 350 mg) was treated with MCPBA as previously described for compound **2** to give a mixture of the C(14) epimeric 14,15-epoxy derivatives (355 mg). This mixture was treated in a Et_2O solution with $LiAlH_4$ in the usual manner yielding a mixture of the C(14) epimers **8** and **9**, which was chromatographed [silica gel column, $CHCl_3$–MeOH (49:1)], yielding pure **8** (100 mg) and **9** (123 mg).

8: mp 209–210 °C (Me_2CO–*n*-hexane); $[\alpha]^{20}_D$ −24.3° (*c* 0.31, MeOH); IR (KBr) 3475, 3405, 3350 (hydroxyl groups), 3020, 2930, 2880, 1465, 1390, 1050, 1035, 1000, 960, 945, 915 cm^{-1}; ^{1}H NMR δ 4.33 (1 H, dd, $J_{aa'}$ = 10 Hz, $J_{ae'}$ = 6 Hz, H-12), 3.84 (1 H, q, J = 6 Hz, H-14), 3.38 (1 H, dd, $J_{aa'}$ = 9 Hz, $J_{ae'}$ = 6 Hz, H-3), 1.31 (3 H, d, J = 6 Hz, 3H-15), CMe singlets at 1.47, 1.19, 1.12, 0.96, and 0.77; mass spectrum (EI, 75 eV, direct inlet), *m*/*z* (relative intensity) M$^+$ absent, 325 (M$^+$ − 15, 8), 295 (75), 277 (95), 259 (70), 241 (30), 207 (90), 191 (40), 190 (65), 189 (80), 175 (70), 135 (100), 109 (50), 107 (65), 95 (70), 81 (70), 71 (50), 69 (60). Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.69; H, 10.54.

9: mp 252–253 °C (Me_2CO–*n*-hexane); $[\alpha]^{20}_D$ −26.6° (*c* 0.30, MeOH); IR (KBr) 3410, 3360, 3300 (hydroxyl groups), 3010, 2940, 2880, 1455, 1390, 1380, 1360, 1090, 1045, 1000, 990, 915 cm^{-1}; ^{1}H NMR δ 4.62 (1 H, q, J = 6 Hz, H-14), 3.87 (1 H, dd, $J_{aa'}$ = 10 Hz, $J_{ae'}$ = 4.5 Hz, H-12), 3.36 (1 H, dd, $J_{aa'}$ = 9 Hz, $J_{ae'}$ = 6 Hz, H-3), 1.33 (3 H, d, J = 6 Hz, 3H-15), CMe singlets at 1.30, 1.20, 1.10, 0.89, and 0.70; mass spectrum (EI, 75 eV, direct inlet), *m*/*z* (relative intensity) M$^+$ absent, 325 (M$^+$ − 15, 5), 295 (95), 277 (100), 259 (70), 241 (40), 207 (90), 191 (40), 190 (80), 189 (60), 175 (60), 135 (90), 109 (40), 107 (40), 95 (40), 81 (60), 71 (40), 69 (70). Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.31; H, 10.37.

Application of Horeau's Method[6] to Compounds 6, 8, and 9. Compound **6** (28.55 mg, 0.089 mmol) and APBA (see above, 165.75 mg, 0.5346 mmol) in pyridine solution (2.00 mL): $\alpha_1 - 1.1\alpha_2$ = +0.028 for the 3*R* and 12*S* centers. Compound **8** (30.26 mg, 0.089 mmol) and APBA (165.75 mg, 0.5346 mmol) in pyridine solution (2.00 mL): $\alpha_1 - 1.1\alpha_2$ = +0.230 for the 3*R*, 12*S*, and 14 centers; thus, 0.230 − 0.028 = +0.202 for the C(14)-hydroxyl group, configuration 14*R*. Compound **9** (30.27 mg, 0.089 mmol) and APBA (165.75 mg, 0.5346 mmol) in pyridine solution (2.00 mL): $\alpha_1 - 1.1\alpha_2$ = −0.156 for the 3*R*, 12*S*, and 14 centers; thus, −0.156 − 0.028 = −0.184 for the C(14)-hydroxyl group, configuration 14*S*. This experiment was performed with identical time reaction (17 h) and temperature (20 °C) for the three compounds.

Acknowledgment. We thank Professor A. García-Granados, Department of Organic Chemistry, University of Granada, Spain, for providing the samples of compounds **1** and **5**, and Miss M. D. Casado and Mrs. M. Plaza, our Institute, for recording the ^{13}C NMR spectra. This work was supported in part by the Comisión Asesora de Investigación Científica y Técnica, Madrid (Grant No. 11/1981).

Registry No. **2**, 88143-08-2; **3**, 92346-75-3; **3** (borate), 92346-74-2; **4**, 92419-32-4; **4** (borate), 92419-27-7; **5**, 88143-09-3; **6**, 92419-30-2; **7**, 92419-31-3; **8**, 92419-33-5; **8** (borate), 92419-28-8; **9**, 92419-34-6; **9** (borate), 92419-29-9.

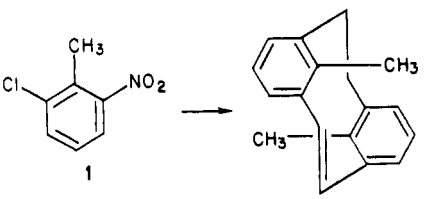
Selective Preparation. 40. A New Preparative Route to 8,16-Dimethyl[2.2]metacyclophan-1-ene[1]

Masashi Tashiro,* Takehiko Yamato, and Kazumasa Kobayashi

Research Institute of Industrial Science and Department of Molecular Science and Technology, Graduate School of Engineering Sciences, Kyushu University 86, Sakamoto, Kasuga, Kasuga-shi, Fukuoka 816, Japan

Received November 30, 1983

Although Boekelheide and his co-workers reported a synthesis of 8,16-dimethyl[2.2]metacyclophan-1-ene (**2**) in low total yield from 2-chloro-6-cyanotoluene (**1**) by a sequence including 13 steps, the starting compound **1** is not readily available.[2,3]



1 2

We now report a convenient preparation of **2** in 12 steps from *p*-*tert*-butyltoluene (**3**) involving the use of *tert*-butyl group as a positional protective group (Scheme I).

The preparation of 2-bromo-4-*tert*-butyltoluene (**4**) from **3** was described in the previous reports.[4] The titanium(IV) chloride catalyzed chloromethylation of **4** with chloromethyl methyl ether afforded the chloride **5** in 73% yield, which was converted to **6** by Grignard reaction. When **6** was treated with aluminum chloride in benzene, the desired **7** was obtained in 75% yield together with **8**. Compound **7** was treated with *n*-butyllithium in ether followed by treatment with dry ice to give **9** in 69% yield.[2] The desired dichloride **12** was easily obtained from **9** via **10** and **11** in the usual manner.[2] Reaction of **12** with sodium

(1) Part 41: Tashiro, M.; Yoshiya, H., submitted for publication.
(2) Lindsay, W. S.; Stokes, P.; Fumber, L. G.; Boekelheide, V. *J. Am. Chem. Soc.* **1961**, *83*, 943.
(3) Blaschke, H.; Ramey, C. E.; Calder, I.; Boekelheide, V. *J. Am. Chem. Soc.* **1970**, *92*, 3675.
(4) Tashiro, M.; Yamato, T. *J. Chem. Soc. Perkin Trans. 1* **1979**, 176.

0022-3263/84/1949-4724$01.50/0