Synthesis of C-17-Functionalized Beyerane Diterpenes. Synthesis of (−)-Erythroxylol B, (−)-Erythroxydiol A and (−)-Benuol

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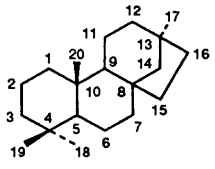
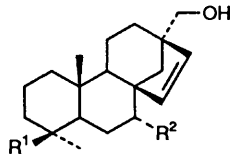
The title compounds **1**, **2** and **3** became accessible from an appropriately functionalized podocarpenone **4** in short sequences of operations, in which the key step involves the toluene-*p*-sulfonic acid-induced rearrangement of 13-epimeric epoxides **6** and **7**.

The presence of a bridgehead hydroxymethyl group at C-13 is unique to some tetracyclic diterpenes of the beyerane group.[1] Erythroxylol B **1**, isolated from *Erythroxylon monogynum*,[2a] erythroxydiol A **2**, isolated from *Erythroxylon monogynum*,[2a] *Helichrysum dendroideum*,[2b] and *Baccharis tola*,[2c] and benuol **3**, isolated from *Sideritis serrata*,[2d] are some representative examples of beyeranes containing this characteristic moiety.†



beyerane skeleton



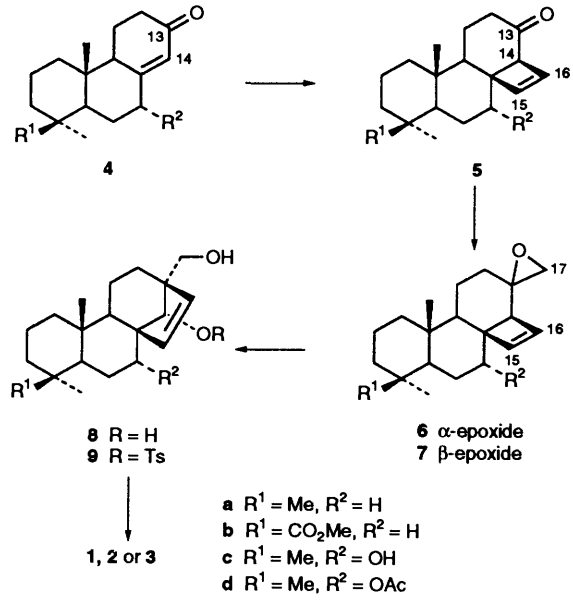
1 R^1 = Me, R^2 = H
2 R^1 = CH_2OH, R^2 = H
3 R^1 = Me, R^2 = OH

In the course of our studies on the synthesis of spongian pentacyclic diterpenes we have reported[3] a novel skeletal rearrangement of a bicyclo[4.2.0]octane system that permits the conversion of a podocarpane system into a C-17-functionalized beyerane compound by a simple three-step procedure. We have continued to explore the utility and scope of this reaction and describe herein its application to the synthesis of the above mentioned beyerane diterpenes: erythroxylol B **1**, erythroxydiol A **2** and benuol **3**. These diterpenes have received little attention from a synthetic standpoint, only the synthesis of diol **2** from steviol having been reported so far.[4]

Our synthesis of these compounds, which is illustrated as a general case in Scheme 1, begins with an appropriately functionalized podocarpenone **4**, which after stereoselective photocycloaddition of acetylene and introduction of the epoxymethylene function at C-13 affords key intermediate epoxides **6** and **7**. Their acid-catalysed rearrangement and the reductive removal of the oxygenated function at C-14 complete the synthesis.

Results and Discussion

The first compound to be synthesized was erythroxylol B **1**. This synthesis begins with podocarpenone **4a** which, as shown previously,[3] was transformed into epimeric epoxides **6a** and **7a** following the general sequence outlined above. As described in our previous work, these epoxides proved to be rather unstable and, although they could be purified for NMR characterization,



4 **5** **8** R = H **9** R = Ts **6** α-epoxide **7** β-epoxide

1, 2 or 3

a R^1 = Me, R^2 = H
b R^1 = CO_2Me, R^2 = H
c R^1 = Me, R^2 = OH
d R^1 = Me, R^2 = OAc

Scheme 1

the crude mixture was usually carried forward so as to avoid extensive loss of material.

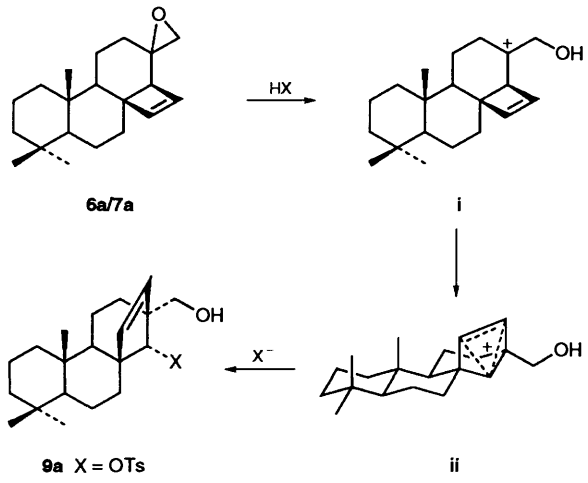
The first conditions we used to rearrange these epoxides involved their treatment with a catalytic amount of a Lewis acid (BF_3·Et_2O) in wet dichloromethane. Under these conditions, the rearrangement of either epoxide **6a** or **7a**, or the mixture of both, gave the beyerene diol **8a** in ~ 70% yield. As previously mentioned,[3] the reaction occurs through an acid-catalysed opening of the oxirane ring to give a carbocation (**i** in Scheme 2), followed by migration of bond C(16)–C(14) to C(16)–C(13) together with attack on C-14 by water.

Although erythroxylol B **1** would be available from diol **8a** *via* reduction of the C-14 hydroxy group, the presence of a second hydroxy group in the molecule could make this transformation problematic. A more suitable intermediate should be one having an easily removable group at C-14. We reasoned that if the above rearrangement were effected in an anhydrous medium using a protic acid (HCl, HOTs, *etc.*) as catalyst, the intermediate non-classical carbonium ion formed at C-14‡ (**ii** in

† The nomenclature and numbering system used throughout this paper are the usual in the terpene field; see ref. 1. The absolute stereochemistry showed in formulae **1**–**3** corresponds to those of the compounds prepared in this paper; natural erythroxylol B, erythroxydiol A and benuol belong to the *ent*-beyerane family and are therefore antipodal of those shown here (*vide infra*).

‡ The homoaromatic character of this cation and its structural analogy with the 7-norbornenyl cation is supported by *ab initio* calculations (6-31G* basis set). The stabilization due to the interaction of the double bond with the positive charge, evaluated by an isodesmic reaction (MP2/6-31G*//6-31G*) is ~ 13 kcal mol^{-1} (1 cal = 4.184 J), similar to that calculated for the 7-norbornenyl cation.[5] The optimized geometry of this cation (see species **iii** in Scheme 3) gives atomic distances and angles [C(14)–C(15) = C(14)–C(16) = 1.8 Å; C(15)–C(8)–C(14) = C(16)–C(13)–C(14) = 73°] similar to those of 7-norbornenyl cations, which explains the observed stereoselectivity in its reaction with nucleophiles.

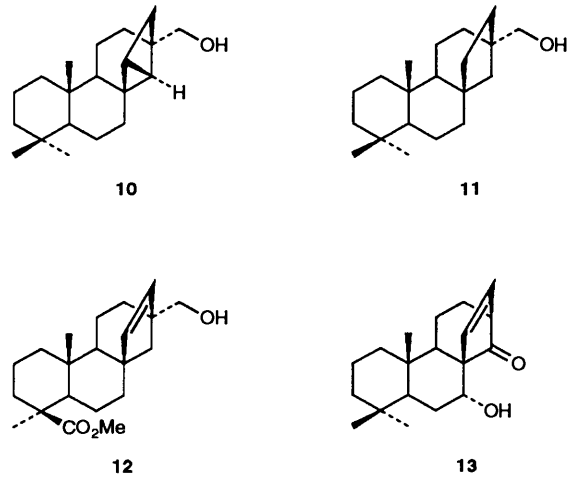
Scheme 2) might be neutralized by the conjugated base of the acid, thus giving distinct functionalities at C-14 and C-17 which should facilitate the required reduction of the former.



Scheme 2

Following the necessary investigations of conditions to effect the above rearrangement in the absence of water, we found that the required transformation could efficiently be effected by treatment of epoxide **6a** and/or **7a** with an excess of anhydrous toluene-*p*-sulfonic acid (PTSA) in diethyl ether at 0 °C. Instead of the 14,17-diol **8a** the 14α-tosyloxy-17-hydroxy compound **9a** was obtained in 60–70% yield. On occasions, a variable amount of diol **8a** was obtained from the above reaction but its formation could be prevented by careful drying of the monohydrated PTSA used and by effecting the reaction in the presence of freshly activated 3 Å molecular sieves. The stereochemistry at C-14 of product **9a** followed from a comparison of the ^{13}C NMR spectra of compounds **9a** and **8a**. In these compounds C-9 and C-12 appear at approximately the same chemical shift, shifted upfield (between 8 and 10 ppm) with regard to the same carbon atom of other beyeranes in which the oxygenated function at C-14 is absent (*e.g.*, **1**).[6]

Completion of the synthesis of erythroxylol B **1** was realized by reductive removal of the secondary 14α-tosyloxy group. Thus, treatment of compound **9a** with sodium iodide and activated zinc dust in hexamethylphosphoric triamide (HMPA)[7] at 105 °C afforded directly the crystalline compound **1** in 83% yield after column chromatography. Attempts to reduce ester **9a** by means of lithium aluminium hydride led to complex product mixtures. Only when a clear solution of $LiAlH_4$ in refluxing THF* was used did a clear reaction take place to afford, nearly exclusively, a chromatographically inseparable 3:7 mixture of the desired beyerane **1** and the highly strained pentacyclic compound **10**. This result, which has a related precedent in the reduction of 7-norbornenyl derivatives,[8] can be explained by admitting an initial solvolysis of the tosyl ester **9a** to form the non-classical cation **iii** (Scheme 3), which is then followed by, probably, intramolecular addition of hydride to C-16 to give pentacycle **10** or to C-14 to give erythroxylol B **1**. The structure of compound **10** was assigned as such on the basis of its ^1H and ^{13}C NMR data, obtained from a small amount of nearly pure compound **10** achieved by chemical degradation of the minor compound **1** from the mixture of both (see Experimental section). In particular, the ^1H and ^{13}C spectra (see Table 1) showed signals corresponding to the two methine moieties of the cyclopropane ring [14-H/C-14, at δ 1.17 (dd, *J* 5.3 and 1.7 Hz)/δ_C 25.90; 15-H/C-15 at δ 1.23 (dd, *J* 5.3 and 4.5 Hz)/δ_C 24.32] and the methylene group of the cyclobutane ring (two 16-H at δ 1.65; C-16 at δ_C 25.86).† Further support for the structural assignment of compound **10**



was obtained from the chemical conversion of the 3:7 mixture of compounds **1** and **10** into the known saturated beyeran-17-ol[2a] **11** when subjected to standard hydrogenation conditions.

The synthesis of the second target compound, erythroxydiol A **2**, was carried out by an analogous sequence of steps starting from podocarpenone **4b**.[9] Thus, irradiation of enone **4b** in dry acetone saturated with acetylene at −30 °C gave the cyclobutenone **5b** in ~50% yield. Its treatment with dimethylsulfonium methylide afforded a chromatographically inseparable mixture of C-13 epimeric epoxides, **6b** and **7b**, which were not purified owing to their instability to silica gel but were rearranged under similar conditions as described above for epoxides **6a**/**7a**. By this means the 14α-tosyloxy-17-hydroxy compound **9b** was obtained in ~70% yield from cyclobutenone **5b**. Subsequent reductive removal of the tosyloxy moiety in compound **9b** was brought about by activated zinc and sodium iodide in HMPA at 105 °C to give compound **12** in 84% yield. Finally, lithium aluminium hydride reduction of methyl ester **12** afforded the crystalline diol **2** in 95% yield.

The synthesis of the third target molecule, benuol **3**, began with the incorporation of the hydroxy function at C-7 through the transformation of the enone **4a** into the corresponding 7,13-dienyl acetate under standard conditions. Its oxidation with *m*-chloroperbenzoic acid (MCPBA), gave the hydroxy enone **4c** in 72% yield from the starting enone. Irradiation of compound **4c** in dry acetone saturated with acetylene at −30 °C yielded the expected cyclobutene **5c** in 63% yield.

The next step, addition of methylene to the carbonyl group of compound **5c**, was surprisingly troublesome. Since direct reaction of keto alcohol **5c** with dimethylsulfonium methylide under the usual conditions only returned unchanged starting material we considered the protection of the hydroxy function at C-7. Several protective groups were evaluated, such as tetrahydropyranyl ether, triisopropylsilyl ether, methyl ether

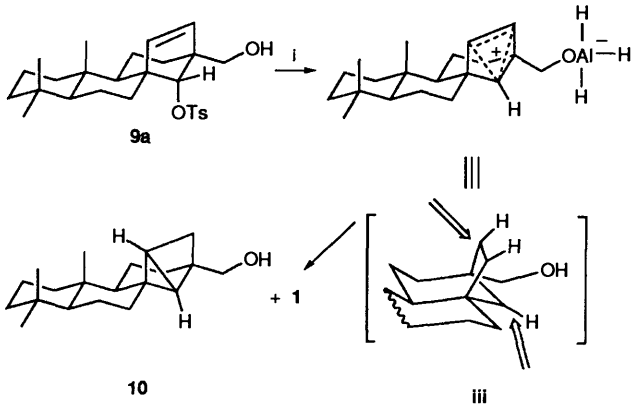
* Treatment of sulfonate **9a** with $LiAlH_4$ in THF at room temperature gave complex product mixtures from which only diol **8a** could be isolated in very low yield.

† Complete assignments of ^1H and ^{13}C NMR data for this compound were made on the basis of a combination of DEPT, HMQC and NOE experiments. Of special significance was the NOE effect observed between 7-H^β (irradiated) and the protons at C-14 and C-15, as well as the NOE enhancement observed between 17-H (irradiated) and the protons at C-14 and C-16. Mention should be made of the unusually low chemical shift of 7-H^β (δ 0.59), a consequence of its situation within the shielding region of the cyclopropane ring.

Table 1 ^{13}C Chemical shifts (δ_C in ppm from $SiMe_4$) of compounds mentioned in the Experimental section[a]

	1	2	3	5b	5d	9a[b]	9b[c]	9c[d]	10	11	12	13
C-1	39.12	39.15	38.92	39.19	38.59	38.77	39.16	39.06	38.46	39.71	39.50	39.00
C-2	18.59	18.24	18.53	19.10	18.39	18.41	19.11	18.52	18.84	18.45	19.25	18.54
C-3	42.06	35.56	41.94	38.08	41.86	41.75	37.83	41.79	42.31	42.00	38.11	41.68
C-4	33.16	38.51	32.65	43.90	32.73	33.94	43.71	32.59	33.35	33.16	43.86	32.57
C-5	55.97	56.77	46.92	56.67	48.21*	55.17	56.19	45.75	56.75	56.52	56.97	45.47
C-6	20.07	20.17	27.55†	22.07	24.63	21.05	20.95†	27.45	21.47	20.22*	21.60	27.08
C-7	37.10	37.47	73.24	38.71	75.78	32.45	32.89	72.48	37.36	41.12	37.40	69.71
C-8	48.65	48.62*	53.98*	53.55	55.54	48.97	49.04*	53.36*	25.79	44.92†	48.71*	56.07
C-9	53.35	53.45	47.53	54.07	49.05*	45.22	44.56	40.35	49.71	57.29	52.72	50.12*
C-10	37.35	37.31	37.42	38.58	38.02	36.95	37.44	37.51	38.70	37.77	37.70	38.59
C-11	19.55	19.75	19.17	18.62	17.45	19.26	20.78†	17.64	19.50	19.76*	19.81	17.52
C-12	27.81	27.81	27.76†	40.10	40.15	18.01	18.30†	22.06	26.90	32.59‡	27.70	26.22
C-13	49.98	50.00*	50.35*	212.87	211.14	50.39	50.51*	51.50*	38.43	44.68†	50.01*	50.59*
C-14	55.57	55.49	51.26	63.11	59.58	85.89	85.75	83.70	25.90	52.32	55.39	222.63
C-15	137.47	137.12	135.56	146.72	143.80	135.11	134.61	134.04	24.32	33.04	136.83	132.75
C-16	131.64	131.94	133.15	132.67	135.23	130.83	131.19	131.79	25.86	34.58‡	131.94	127.78
C-17	68.66	68.63	68.47			64.12	64.17	64.15	70.77	71.05	68.62	
C-18	33.65	27.02	33.38	28.78	33.11	33.42	28.80	33.36	33.68	33.69	28.93	33.33
C-19	21.92	65.53	21.88	177.68	21.32	21.82	177.81	21.07	21.95	21.91	178.04	22.02
C-20	15.03	15.73	14.53	13.09	14.48	15.49	14.11	15.36	13.70	15.14	13.59	15.23
CO_2Me				51.23			51.19				51.16	
Me Ar						21.63	21.67	21.72				
OCO*Me*					21.32							
OCOMe					170.33							

[a] At 75.4 MHz in $CDCl_3$. The signals with the same superscript may be interchanged within the same column. [b] Ar signals at δ_C 144.92 (C), 133.84 (C), 127.87 (2 × CH) and 129.69 (2 × CH). [c] Ar signals at δ_C 144.99 (C), 133.87 (C), 127.91 (2 × CH) and 129.75 (2 × CH). [d] Ar signals at δ_C 144.98 (C), 133.86 (C), 129.82 (2 × CH) and 127.90 (2 × CH).



Scheme 3 *Reagents and conditions:* i, $LiAlH_4$, THF, reflux

and trifluoroacetate, but none was very promising in our attempts to introduce the epoxymethylene function at C-13 using dimethylsulfonium methylide.* Either no reaction occurred or an intractable mixture of polar compounds was formed, depending on the reaction conditions and the protective group used. For reasons we cannot explain, the only effective protective group was the acetate. Although the reaction of keto acetate **5d**, prepared from the alcohol **5c** by reaction with acetic anhydride and a catalytic amount of 4-pyrrolidinopyridine in dry triethylamine under standard conditions, with dimethylsulfonium methylide proceeded smoothly to give the expected epoxide as a mixture of 13-epimers (**6d** and **7d**), the reaction was complicated by partial hydrolysis of the acetate moiety. Owing to this fact and to the marked instability to silica gel of these compounds, isolation of a pure product was possible only after hydrolysis of the acetate group and acid-catalysed rearrangement of the epoxymethylene moiety. Thus, treatment of the crude mixture obtained from the reaction of keto acetate **5d** with dimethylsulfonium methylide with cold methanolic sodium methoxide followed by subsequent TsOH-induced rearrangement afforded the desired 14α-tosyloxy-7,17-dihydroxy compound **9c** in ~30% overall yield (three steps). For reasons that are not obvious, exchange in the order of the last two steps resulted in complex product mixtures containing little, if any, compound **9c**.

Finally, treatment of diol **9c** with activated zinc dust and sodium iodide in the same manner as described for compounds **9a** and **9b** afforded the beyerane diterpene benuol **3** in 81% yield.

Synthetic erythroxylol B **1**, erythroxydiol A **2**, and benuol **3** exhibited spectroscopic and physical data identical with those previously reported for the natural products;[2a–d,13] the only difference was in the sign of the optical rotation, which shows that natural and synthetic compounds are therefore antipodal.[4,14]

Experimental

General conditions are as described previously.[15]

Preparation of Cyclobutenes **5a**, **5b** *and* **5c**.—Cyclobutenes **5a** and **5c** were prepared readily by photoaddition of acetylene to the appropriate 8(14)-podocarpen-13-one such as is described in refs. 3 and 15, respectively. Following the same procedure the podocarpenone **4b**[9] (218 mg, 0.69 mmol) provided the cyclobutene **5b** (108 mg, ~50%) after column chromatography using hexane–ethyl acetate (9:1) as eluent. The *cyclobutene* **5b** was recrystallized from hexane, as needles, m.p. 138–139 °C (from hexane) (Found: C, 75.9; H, 9.1. $C_{20}H_{28}O_3$ requires C, 75.91; H, 8.92%); $[\alpha]_D^{23}$ +252 (*c* 2.7, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3050, 1720, 1695, 1225, 1155, 975 and 795; δ_H(300 MHz) 6.56 (1

* The use of (bromomethyl)lithium[10] for the preparation of the oxirane moiety gave a complex reaction mixture. Attempts to prepare it *via* iodomethylation of compound **5c** by treatment with diiodomethane and samarium[11] gave the rearranged ketone **13** as the only identified compound. The latter reaction, which probably follows a radical-promoted reaction pathway, parallels the previously reported acid-catalysed rearrangement of related systems.[12]

H, d, *J* 2.7, 15-H), 6.02 (1 H, dd, *J* 2.7 and 1.2, 16-H), 3.64 (3 H, s, CO_2Me), 2.91 (1 H, br s, 14-H), 2.62 (1 H, dddd, *J* 19, 5.9, 1.7 and 0.7, 12-H^{β}), 2.17 (1 H, dddd, *J* 19, 11, 8.3 and 2, 12-H^{α}), 2.17 (1 H, m, 3-H^{β}), 1.19 (3 H, s, 4-Me^{α}), 1.20 (1 H, dd, *J* 12.6 and 2.7, 5-H), 1.14 (1 H, dd, *J* 11.8 and 3.2, 9-H) and 0.67 (3 H, s, 10-Me^{β}); *m/z* (CI) 317 ($M^+ + 1$, 100%), 316 (M^+, 8), 300 (6), 299 (34), 257 (12) and 239 (7); δ_C see Table 1.

Conversion of Compound **5a** *into* 14α-*Tosyloxybeyer*-15-*en*-17-*ol* **9a**.—A solution of the crude 4:6 mixture of epoxides **6a** and **7a** (77.8 mg, 0.27 mmol), obtained by reaction of ketone **5a** (76.7 mg, 0.28 mmol) with dimethylsulfonium methylide in tetrahydrofuran (THF)–HMPA as described in ref. 3, in dry diethyl ether (1 cm^3) was added dropwise to an ice-cooled solution of anhydrous PTSA[16] (600 mg, 3.5 mmol) in diethyl ether (1 cm^3) containing freshly activated 3 Å molecular sieves (1 g). After being stirred at the same temperature for 5 min, the mixture was diluted with diethyl ether and filtered. The filtrate was washed successively with aq. sodium carbonate and brine, dried, and then evaporated to dryness to give an oily residue which, after column chromatography with hexane–ethyl acetate (9:1) as eluent, gave the *hydroxy sulfonate* **9a** (76.1 mg, 61% from **5a**) as an amorphous solid (Found: C, 70.4; H, 8.3; S, 6.6. $C_{27}H_{38}O_4S$ requires C, 70.71; H, 8.35; S, 6.99%); $[\alpha]_D^{24}$ −34 (*c* 2.7, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3550, 3050, 1595, 1190, 1175, 940, 855 and 750; δ_H(200 MHz) 7.81 (2 H, d, *J* 8.3, ArH), 7.33 (2 H, d, *J* 8.3, ArH), 5.76 (1 H, d, *J* 6.5, 15-H), 5.62 (1 H, d, *J* 6.5, 16-H), 4.24 (1 H, s, 14-H), 3.43 (2 H, br s, 17-H_2), 2.43 (3 H, s, Ar*Me*), 0.77, 0.74 and 0.70 (9 H, 3 s, 4-Me_2 and 10-Me^{β}); *m/z* (CI) 459 ($M^+ + 1$, 0.8%), 458 (M^+, 0.5), 315 (2), 289 (3), 288 (24), 287 (100), 285 (10), 271 (5) and 269 (6); δ_C see Table 1.

Beyer-15-*en*-17-*ol* [(−)-*Erythroxylol B*] **1**.—A mixture of tosyl ester **9a** (29.2 mg, 0.064 mmol), sodium iodide (114.6 mg, 0.76 mmol), freshly activated zinc powder (100 mg, 1.53 mmol) and dry HMPA (0.8 cm^3) was stirred, under argon, for 27 h at 105–110 °C. The reaction mixture was filtered to remove excess of sodium iodide and zinc powder. The filtrate was poured into water and extracted with diethyl ether. The combined extracts were washed successively with water, aq. $Na_2S_2O_3$ and brine, dried, concentrated and chromatographed on silica gel with hexane–ethyl acetate (9:1) as eluent, to give the beyerene erythroxylol B **1** (15.3 mg, 83%) as a solid, m.p. 122–123 °C (from hexane) (lit.,[2a] 121.5–123 °C; lit.,[13] 120–122 °C); $[\alpha]_D^{24}$ −48 (*c* 3.1, $CHCl_3$) (lit.,[2a] +67); ν_{max}(KBr)/cm^{-1} 3270, 3060, 1040, 820 and 750; δ_H(400 MHz) 5.80 (1 H, d, *J* 6.5, 15-H), 5.54 (1 H, d, *J* 6.5, 16-H), 3.51 (1 H, d, *J* 10.5, 17-H), 3.42 (1 H, d, *J* 10.5, 17-H'), 1.11 (1 H, ddd, *J* 13.1, 13.1 and 4.2, 3-H^{α}), 1.02 (1 H, dd, *J* 10.8 and 5.5, 9-H), 0.98 (1 H, d, *J* 9.7, 14-H), 0.84 (3 H, s, 4-Me^{α}), 0.80 (3 H, s, 4-Me^{β}) and 0.72 (3 H, s, 10-Me^{β}); δ_C see Table 1.

Lithium Aluminium Hydride Reduction of Tosyl Ester **9a**. *Preparation of Compound* **10**.—To a stirred solution of tosyl ester **9a** (30.6 mg, 0.07 mmol) in THF (0.5 cm^3), was added a 1 mol dm^{-3} solution of $LiAlH_4$ in THF (2.5 cm^3, 2.5 mmol). The reaction mixture was refluxed for 1 h, treated with a 1:1 mixture of THF and water (3 cm^3) and filtered. The filtrate was poured into water and extracted with diethyl ether. The organic phase was washed with brine, dried, and then evaporated to dryness to give the crude product, which was purified by chromatography with hexane–ethyl acetate (9:1) as eluent to afford a chromatographically inseparable 7:3 mixture of pentacyclic compound **10** and beyerene **1** (14.6 mg, 76%). A small amount of nearly pure compound **10** was obtained by chemical degradation of the minor compound **1** from the mixture of both as follows. A solution of the above mixture of products **1** and **10** (7 mg) in dry CH_2Cl_2 (2 cm^3) was slowly bubbled with an O_3/O_2 mixture at −78 °C. Nitrogen was bubbled through the mixture which was then treated with an excess of Me_2S. The reaction was stirred at room temperature overnight, the solvent and the excess of Me_2S were removed under reduced pressure, and the residue was chromatographed using hexane–ethyl acetate (9:1) as eluent to give compound **10** as a solid; $[\alpha]_D^{24}$ −18.5 (*c* 0.54, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3340, 3010, 1450, 1360 and 1025; δ_H(400 MHz) 3.58 (1 H, d, *J* 10.4, 17-H), 3.51 (1 H, d, *J* 10.4, 17-H'), 1.65 (2 H, m, 16-H_2), 1.23 (1 H, dd, *J* 5.3 and 4.5, 15-H), 1.17 (1 H, dd, *J* 5.3 and 1.7, 14-H), 1.05 (3 H, s, 10-Me^{β}), 0.86 (3 H, s, 4-Me^{β}), 0.84 (3 H, s, 4-Me^{α}) and 0.59 (1 H, ddd, *J* 12.7, 3.6 and 2.6, 7-H^{β}); δ_C see Table 1.

Hydrogenation of the Mixture of Compounds **1** *and* **10** *to Give Beyeran*-17-*ol* **11**.—A solution of the 1:3 mixture of compounds **1** and **10** (6 mg) in dry ethyl acetate (2 cm^3) was shaken at room temperature with a catalytic amount of PtO_2 under H_2 for 1 h. Filtration through a short pad of silica gel and evaporation of the solvent afforded beyeran-17-ol **11** (5.9 mg, 98%) as a solid, m.p. 127.5–128.5 °C (from hexane) (lit.,[2a] 128–130 °C); $[\alpha]_D^{24}$ +6 (*c* 1.66, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3350, 1456 and 1030; δ_H(400 MHz) 3.40 (2 H, s, 17-H_2), 2.07 (1 H, dddd, *J* 13.4, 9.3, 4.2 and 2, 15-H^{β}; assigned on the basis of the NOE effect observed with the 10-Me^{β}), 0.98 (1 H, dd, *J* 12 and 4, 9-H), 0.93 (1 H, ddd, *J* 10.9, 2 and 2, 14-H^{α}), 0.91 (3 H, s, 10-Me^{β}), 0.83 (3 H, s, 4-Me^{α}), 0.78 (3 H, s, 4-Me^{β}) and 0.77 (1 H, *J* 12.1 and 2, 5-H); δ_C see Table 1.

Conversion of Ketone **5b** *into Tosyl Ester* **9b**.—A suspension of trimethylsulfonium iodide (67.2 mg, 0.329 mmol) in anhydrous THF (0.7 cm^3)–HMPA (0.8 cm^3) was treated with a 1.2 mol dm^{-3} solution of BuLi in hexane (206 mm^3, 0.329 mmol) at −20 °C. After being stirred at the same temperature for 30 min the mixture was cooled to −40 °C and a solution of ketone **5b** (34.7 mg, 0.11 mmol) in THF (0.8 cm^3) was added dropwise. The resulting yellowish solution was allowed to warm to room temperature and then was stirred for 20 h. The reaction mixture was poured into water and extracted with hexane. The organic phase was washed successively with water and brine, dried, and evaporated to afford a reaction mixture (36.2 mg) whose ^1H NMR spectrum indicated that it was exclusively a 3:7 mixture of the epimeric epoxides **6b** and **7b**, respectively; δ_H(200 MHz) 6.40 (1 H, 2 overlapped d, *J* 2.9 and 2.4, 15-H of both epoxides), 6.23 (1 H, d, *J* 2.9, 16-H of **6b**), 6.02 (1 H, d, *J* 2.9, 16-H of **7b**), 3.61 (3 H, s, CO_2Me of both epoxides), 2.59 (1 H, d, *J* 5.2, 17-H of **6b**), 2.53 (1 H, dd, *J* 5.2 and 1.2, 17-H' of **6b**), 2.50 (1 H, d, *J* 4.6, 17-H of **7b**), 2.47 (1 H, d, *J* 4.6, 17-H' of **7b**), 1.16 (3 H, s, 4-Me^{α} of both epoxides) and 0.61 (3 H, s, 10-Me^{β} of both epoxides).

Following the same procedure used to prepare compound **9a**, tosyl ester **9b** (37 mg, 67% from ketone **5b**) was obtained from the mixture of epoxides **6b** and **7b** obtained above. *Compound* **9b** was obtained as crystals, m.p. 158–160 °C (decomp.) (from hexane–diethyl ether) (Found: C, 66.8; H, 7.5; S, 6.1. $C_{28}H_{38}O_6S$ requires C, 66.91; H, 7.62; S, 6.38%); $[\alpha]_D^{25}$ −11 (*c* 2.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3500, 3060, 1725, 1600, 1185, 950 and 860; δ_H(300 MHz) 7.83 (2 H, d, *J* 8.3, ArH), 7.36 (2 H, d, *J* 8.3, ArH), 5.82 (1 H, d, *J* 6.6, 15-H), 5.65 (1 H, d, *J* 6.6, 16-H), 4.28 (1 H, s, 14-H), 3.60 (3 H, s, CO_2Me), 3.40 (2 H, br s, 17-H_2), 2.46 (3 H, s, Ar*Me*), 2.13 (1 H, m, 3-H^{β}), 1.12 (3 H, s, 4-Me^{α}) and 0.54 (3 H, s, 10-Me^{β}); *m/z* (CI) 503 ($M^+ + 1$, 2%), 502 (M^+, 6), 391 (2), 377 (4), 350 (11), 349 (50), 332 (24) and 331 (100); δ_C see Table 1.

Beyer-15-*ene*-17,19-*diol* [(−)-*Erythroxydiol A*] **2**.—A stirred mixture of tosyl ester **9b** (25.2 mg, 0.05 mmol), NaI (90 mg, 0.6 mmol) and zinc (79 mg, 1.2 mmol) in HMPA (0.8 cm^3) was heated at 105 °C for 27 h. Following the same work-up as used to prepare compound **1**, the *hydroxy ester* **12** (14 mg, 84%) was obtained as a solid, m.p. 99–100 °C (from hexane) (Found: C, 75.5; H, 9.6. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%); $[\alpha]_D^{26}$ −14

(*c* 0.7, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3340, 3050, 1725, 1235, 1155, 810 and 750; δ_H 5.83 (1 H, d, *J* 5.9, 15-H), 5.55 (1 H, d, *J* 5.9, 16-H), 3.62 (3 H, s, CO_2Me), 3.53 (1 H, d, *J* 10.7, 17-H), 3.43 (1 H, d, *J* 10.7, 17-H'), 2.14 (1 H, m, 3-H$^{\beta}$), 1.16 (3 H, s, 4-Me$^{\alpha}$) and 0.55 (3 H, s, 10-Me$^{\beta}$); *m/z* (CI) 334 (M^+ + 2, 2%), 333 (M^+ + 1, 10), 331 (3), 315 (4), 103 (11), 101 (17), 87 (11), 85 (66) and 83 (100); δ_C see Table 1.

To a stirred suspension of $LiAlH_4$ (32 mg, 0.84 mmol) in anhydrous diethyl ether (0.2 cm^3) was added a solution of hydroxy ester **12** (11 mg, 0.033 mmol) in diethyl ether (0.4 cm^3). After being stirred for 3 h at room temperature, the reaction mixture was cooled to 0 °C and treated with a few drops of water and 15% aq. sodium hydroxide. The mixture was diluted with diethyl ether and filtered. The filtrate was washed successively with water and brine, dried, and evaporated to afford a residue, which was purified by chromatography using hexane–ethyl acetate (6:4) as eluent to give erythroxydiol A **2** (9.6 mg, 95%) as a solid, m.p. 184–185 °C (from ethyl acetate) (lit.,[2a] 179–181 °C; lit.,[13] 180–181 °C); $[\alpha]_D^{28}$ −49 (*c* 1.2, $CHCl_3$) (lit.,[2a] +60; lit.,[13] +57); ν_{max}(KBr)/cm^{-1} 3290, 3060, 3040, 1035, 1025 and 735; δ_H(300 MHz) 5.77 (1 H, d, *J* 5.7, 15-H), 5.55 (1 H, dd, *J* 5.7 and 1, 16-H), 3.75 (1 H, d, *J* 11, 19-H), 3.52 (1 H, d, *J* 10.8, 17-H), 3.43 (1 H, d, *J* 10.8, 17-H'), 3.42 (1 H, dd, *J* 11 and 1.2, 19-H'), 1.77 (1 H, dddd, *J* 13.7, 3.3, 3.3 and 1.6, 3-H$^{\beta}$), 0.98 (1 H, d, *J* 10, 14-H), 0.95 (3 H, s, 4-Me$^{\alpha}$), 0.86 (1 H, ddd, *J* 13, 13 and 4.4, 1-H$^{\alpha}$) and 0.71 (3 H, s, 10-Me$^{\beta}$); δ_C see Table 1.

Conversion of Ketone **5c** *into Tosyl Ester* **9c**.—To a mixture of the hydroxy ketone **5c**[15] (100 mg, 0.348 mmol), a crystal of 4-pyrrolidinopyridine, and triethylamine (1 cm^3) was added acetic anhydride (138 mm^3, 0.146 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the mixture was diluted with CH_2Cl_2 and washed successively with dil. hydrochloric acid, water, and brine, dried, and then evaporated to dryness. The resulting residue was purified by chromatography, with hexane–ethyl acetate (9:1) as eluent, to afford the acetate **5d** (107 mg, 93%) as a solid, m.p. 139–140 °C (from hexane); $[\alpha]_D^{24}$ +178 (*c* 2.7, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3045, 1735, 1690, 1240, 1030, 825 and 790; δ_H(300 MHz) 6.38 (1 H, dd, *J* 2.8 and 0.5, 15-H), 6.10 (1 H, dd, *J* 2.8 and 1.3, 16-H), 4.94 (1 H, dd, *J* 2.8 and 2.8, 7-H), 2.99 (1 H, br s, 14-H), 2.62 (1 H, dddd, *J* 19.1, 5.3, 2 and 1, 12-H$^{\beta}$), 2.21 (1 H, dddd, *J* 19.1, 10.9, 7.8 and 1.7, 12-H$^{\alpha}$), 2.03 (3 H, s, OAc), 1.18 (1 H, ddd, *J* 13.7, 13.7 and 4.5, 3-H$^{\alpha}$), 1.00 (1 H, ddd, *J* 12.6, 12.6 and 4, 1-H$^{\alpha}$) and 0.84, 0.80 and 0.78 (3 H each, each s, 4-Me_2 and 10-Me$^{\beta}$); *m/z* (CI) 331 (M^+ + 1, 3%), 330 (M^+, 1), 299 (5), 273 (3), 272 (22), 271 (100), 269 (7), 253 (25), 244 (20) and 243 (92); δ_C see Table 1.

A mixture of the above acetate **5d** (64.4 mg, 0.195 mmol) and dimethylsulfonium methylide [from trimethylsulfonium iodide (119.4 mg, 0.58 mmol) and a 1.2 mol dm^{-3} solution of BuLi in hexane (366 mm^3, 0.58 mmol)] in THF (2.6 cm^3)–HMPA (1.5 cm^3) was allowed to warm from −40 °C to room temperature and was then stirred for 14 h. Following the same work-up procedure used to prepare compounds **6b**/**7b**, a crude reaction mixture was obtained (59 mg), whose ^1H NMR spectrum indicated that it was a mixture of the epimeric acetate epoxides **6d**/**7d** [signals at δ_H 5.01 and 4.93 (two t corresponding to 7-H of both isomers)] and the alcohol epoxides **6c**/**7c** [signals at δ_H 3.81 and 3.77 (two t corresponding to 7-H of both isomers)], the latter formed by partial saponification of the acetate moiety of the former. The above mixture was dissolved in MeOH (1.3 cm^3) and treated with a solution of NaOMe in MeOH [1.2 cm^3 of a solution prepared from Na (100 mg) in MeOH (2.5 cm^3)] at −15 °C. After being stirred at the same temperature for 4 h, the mixture was diluted with diethyl ether, washed successively with water and brine, dried, and evaporated to afford a residue (58.8 mg) whose ^1H NMR spectrum showed it to be essentially a 2:8 mixture of alcohol epoxides **6c** and **7c**.

Following the same procedure used to prepare compound **9a**, tosyl ester **9c** (27.8 mg, 30% from the ketone **5d**) was obtained from the mixture of epoxides **6c** and **7c** obtained above. Compound **9c** was obtained as an oil, ν_{max}(NaCl)/cm^{-1} 3550, 3050, 1610, 1175, 860 and 740; δ_H(400 MHz) 7.83 (2 H, d, *J* 8.3, ArH), 7.36 (2 H, d, *J* 8.3, ArH), 5.70 (1 H, d, *J* 6.6, 15-H), 5.63 (1 H, d, *J* 6.6, 16-H), 4.87 (1 H, s, 14-H), 3.88 (1 H, dd, *J* 3.2 and 2.5, 7-H), 3.50 (1 H, d, *J* 11.7, 17-H), 3.46 (1 H, d, *J* 11.7, 17-H'), 2.45 (3 H, s, Ar*Me*) and 0.87, 0.80 and 0.76 (3 H each, each s, 4-Me_2 and 10-Me$^{\beta}$); *m/z* 474 (M^+, 0.4%), 317 (3), 304 (8), 303 (34), 301 (8), 285 (34) and 173 (100); δ_C see Table 1.

Beyer-15-ene-7α,17-diol [(−)-*Benuol*] **3**.—A solution of tosyl ester **9c** (20.7 mg, 0.04 mmol) in HMPA (0.5 cm^3) was treated with sodium iodide (78.5 mg, 0.52 mmol) and zinc powder (68.5 mg, 1.05 mmol) as for compound **1**, to give a crude reaction mixture, which was subjected to column chromatography, using hexane–ethyl acetate (9:1) as eluent, to afford the beyerene benuol **3** (10.7 mg, 81%) as a solid, m.p. 116–117 °C (from hexane–CH_2Cl_2) (lit.,[2d] 114–116 °C); $[\alpha]_D^{28}$ −51 (c 0.7, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3450, 3040, 1040 and 760; δ_H(300 MHz) 5.64 (2 H, br s, 15- + 16-H), 3.71 (1 H, dd, *J* 3.0 and 3.0, 7-H), 3.57 (1 H, d, *J* 10.9, 17-H), 3.47 (1 H, d, *J* 10.9, 17-H'), 0.86 and 0.81 (3 H each, each s, 4-Me_2) and 0.73 (3 H, d, *J* 0.6, 10-Me$^{\beta}$); δ_C see Table 1.

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