Synthesis of (–)-Borjatriol

Antonio Abad,* Consuelo Agulló, Manuel Arnó,* Ana C. Cuñat, and Ramón J. Zaragozá

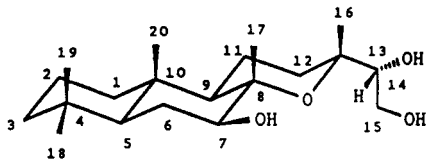
Departamento de Química Orgánica, Universidad de Valencia, Dr. Moliner 50, 46100 Burjasot, Valencia, Spain

Received July 22, 1991

The enantioselective synthesis of (–)-borjatriol ((14*R*)-8,13-epoxylabdane-7β,14,15-triol (**1**)) from (+)-podocarp-8(14)-en-13-one (**2**) is described using as a key step the regioselective intramolecular epoxide ring opening of **13**.

Introduction

Borjatriol (**1**) is a naturally occurring substance of the 8,13-epoxylabdane family isolated from the aerial parts of *Sideritis mugronensis* Borja,[1,2] a wild plant whose infusions have been traditionally used in Spain due to their digestive and antirheumatic properties.[3] During the last decade its pharmacological activity has attracted considerable attention, especially in connection with their antiinflammatory and antiarthritic properties,[4] but no synthetic efforts with borjatriol as the target has yet been reported.[5]



1

We report herein the first synthesis of (–)-borjatriol (**1**) from easily available podocarpenone **2** by a simple stereocontrolled route which is outlined in Scheme I. The key steps of this approach are the asymmetric epoxidation of **10** to give **11** and the acid-catalyzed cyclization of **13** to **14**.

Results and Discussion

Podocarpenone **2**, obtained in optically active form from commercial colophony as described in ref 6, was converted into acetylenic ketone **4** via the epoxy ketone **3** by epoxidation and Eschenmoser ring-opening reaction. Thus, **4** was obtained in 75% overall yield by the reaction of **2** with alkaline hydrogen peroxide followed by treatment of the resulting epoxide **3** with *p*-toluenesulfonohydrazide in methylene chloride in the presence of silica gel, initially at –20 °C and then at room temperature for 4 h. It is worth noting that, as previously reported,[7] Eschenmoser fragmentation of **3** using *p*-toluenesulfonohydrazide in 1:1 acetic acid–methylene chloride proceeds sluggishly, even under forcing conditions, to give the ynone **4** in much lower yield (ca. 40%).[8]

Transformation of ynone **4** into **5** was carried out in one flask in 80% yield by reaction of **4** at low temperature with 2 equiv of methyllithium followed by methoxycarbonylation of the resulting acetylide and alkoxide anions with excess methyl cyanoformate in the presence of added hexamethylphosphoric triamide (HMPA). The configuration at C-8 in **5** was suggested on the basis of its ^{1}H NMR spectrum. The chemical shift of the 10-Me in the ^{1}H NMR spectrum of **5** occurs at δ 0.90 ppm, indicating the presence of a 1,3-diaxial interaction with the carbonate moiety in C-8 which otherwise would result in an upfield shift to δ 0.80 ppm.[9] Difference NOE experiments revealed signal enhancements between 8-Me (irradiated) and H-7β, H-11, and H-12 but no NOE effect between 8-Me and 10β-Me, strongly supporting the α-disposition of the former. This α-orientation of the methyl group at C-8 of **5** is consistent with the general trend for equatorial addition of organometallics to cyclohexanones and with the results obtained in the subsequent syn elimination of the methyl carbonate moiety (vide infra).

Pyrolysis of the methyl carbonate **5** at 210 °C for 30 min gave an approximately 5:1 (by ^{1}H NMR and GC) mixture of $\Delta^{7,8}$ and $\Delta^{8,17}$ olefins **6** and **7**, respectively, in excellent yield (92%). The desired endocyclic olefin **6** was obtained from this mixture in 65% yield by column chromatography on $AgNO_3$–silica gel. Because some material loss occurs during this purification[10] it was more convenient for synthetic purposes to effect the separation of endo and exo olefins after modification of the α,β-acetylenic ester moiety in the subsequent synthetic step (see Experimental Section).

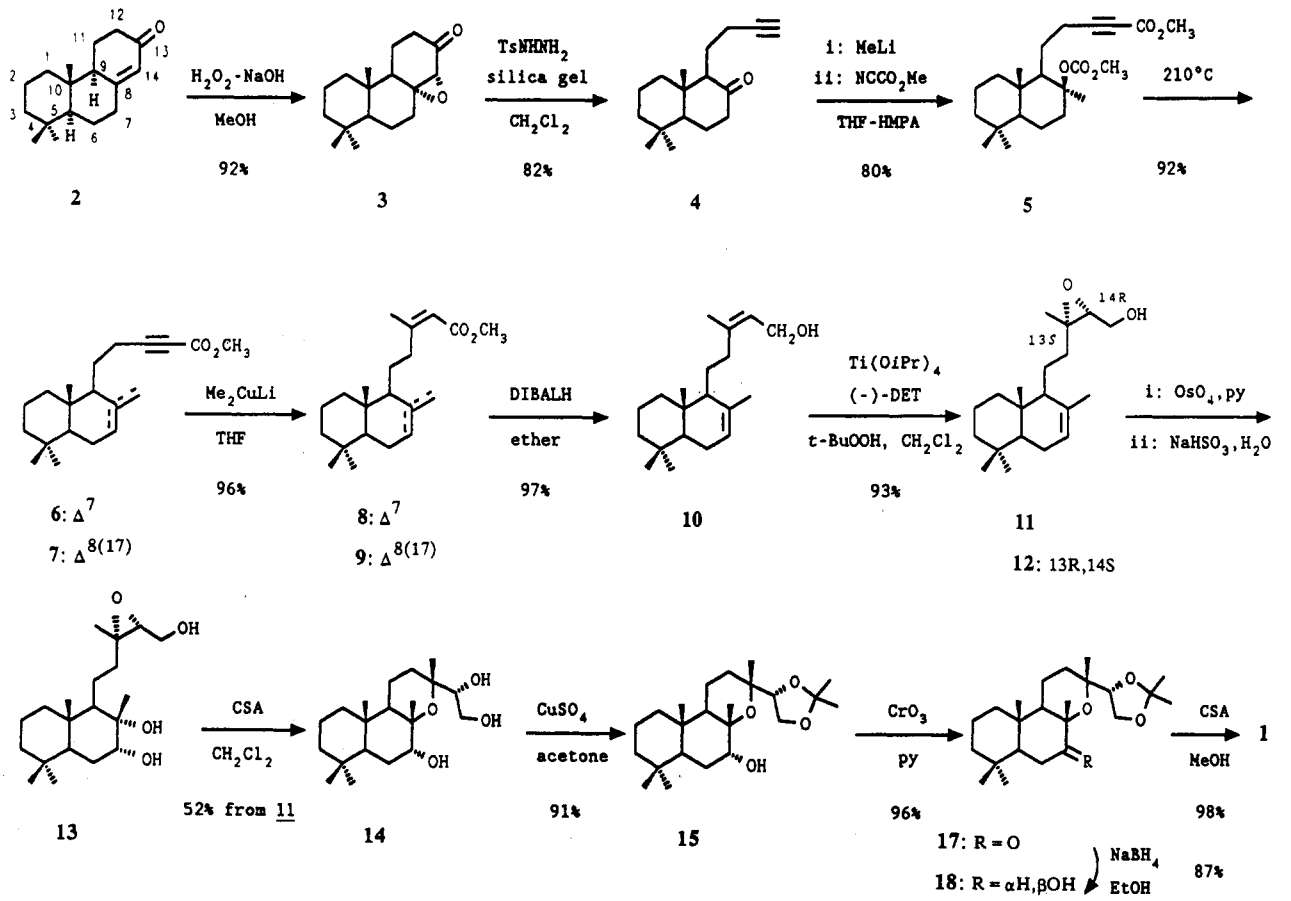
The stereospecific cis addition[11] of lithium dimethylcuprate to the α,β-acetylenic ester moiety of **6** afforded the cis α,β-unsaturated ester **8** in very high yield[12] with no trace, within the limits of the experimental error of the ^{1}H NMR measurement, of the known trans isomer.[13] The next step was the reduction of **8** with diisobutylaluminum hydride (DIBALH), which provided the allylic alcohol needed for the asymmetric epoxidation in nearly quantitative yield.

Stereoselective epoxidation of the allylic alcohol **10** by the asymmetric Sharpless method[14] using D-(–)-diethyl

(1) Rodríguez, B.; Valverde, S. *Tetrahedron* **1973**, *29*, 2837.
(2) Valverde, S.; Rodríguez, B. *Phytochemistry* **1977**, *16*, 1841.
(3) Font Quer, P. *Plantas Medicinales*; Labor: Barcelona, 1980; p 661.
(4) (a) Villar, A.; Salom, R.; Alcaraz, M. J. *Pharmazie* **1983**, *38*, 566. (b) Villar, A.; Salom, R.; Alcaraz, M. J. *Planta Medica* **1984**, 90. (c) Villar, A.; Alcaraz, M. J. *Pharmazie* **1984**, *39*, 278. (d) Barberan, F. A. T.; Mañez, S.; Villar, A. *J. Nat. Prod.* **1987**, *50*, 313. (e) Alcaraz, M. J.; Villar, A. *Pharmazie* **1987**, *42*, 278. (f) Jimenez, A.; Mañez, S.; Villar, A. *Pharmazie* **1990**, *45*, 295.
(5) For some chemical transformation of borjatriol see: (a) Marquez, C.; Rodríguez, B.; Valverde, S. *An. Quím.* **1975**, *71C*, 603. (b) Garcia-Alvarez, M. C.; Rodríguez, B. *J. Org. Chem.* **1981**, *46*, 1915.
(6) Abad, A.; Arnó, M.; Domingo, L. R.; Zaragozá, R. J. *Tetrahedron* **1985**, *41*, 4937.
(7) Grant, P. K.; Rowan, D. D. *Aust. J. Chem.* **1979**, *32*, 1395.
(8) Preliminary experiments with several epoxy ketones have shown that, in comparison, the use of silica gel instead of protic acids as the catalyst for the Eschenmoser fragmentation is advantageous. The mildness of these new conditions coupled with the simplification of the workup procedure might extend conveniently the scope of this synthetically useful reaction.
(9) For ^{1}H NMR of model compounds see: (a) Teresa, J. P.; Urones, I. S.; Nuñez, L.; Basabe, P. *Phytochemistry* **1983**, *22*, 2805. (b) Foster, P. G.; Ghisalberti, E. L.; Jefferies, P. R. *Phytochemistry* **1985**, *24*, 2991. (c) Hirota, H.; Nakamura, T.; Tsuyuki, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4023 and literature cited therein.
(10) Only olefin **6** and a complex mixture of very polar compounds were obtained from this chromatography. It seems that partial decomposition of **6** and complete decomposition of the exocyclic olefin **7** occurs during the chromatographic process.
(11) Krause, N. *Tetrahedron Lett.* **1989**, *30*, 5219 and references contained therein.
(12) The conditions of this reaction were somewhat critical to ensure a good yield of the α,β-olefinic ester. Rigorous exclusion of oxygen as well as the use of freshly purified CuI were needed to avoid the formation of substantial amounts of dimer products; see: Corey, E. J.; Katzenellenbogen, A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
(13) (a) Bewan, C. W. L.; Ekong, D. E. V.; Okogun, J. I. *J. Chem. Soc. C* **1968**, 1067. (b) Imamura, P. M.; Marsaioli, A. J.; Barata, L. E. S.; Ruveda, E. A. *Phytochemistry* **1977**, *16*, 1842.

0022-3263/92/1957-0050$03.00/0

Scheme I



tartrate (-DET) gave the desired 13*S*,14*R* epoxide **11** as a 9:1 mixture of chromatographically inseparable 13*S*,14*R* and 13*R*,14*S* diastereomers **11** and **12**, respectively (93% yield).[15] Unfortunately, compound **11** was not crystalline in our hands and hence its diastereomeric purity could not be enhanced by crystallization. However, this was not a major problem since the corresponding products formed from each diastereomer were very easily separated later in the synthesis (vide infra).

The next step, cis hydroxylation of the 7,8-double bond, was carried out by reaction of **11** with osmium tetraoxide in pyridine followed by hydrolysis of the osmiate ester intermediate with sodium bisulfite. All attempts to purify the epoxy triol **13** by chromatography on silica gel were unsuccessful owing to its marked proclivity to undergo ring closure to tetrahydropyran derivative **14**. Because of this difficulty the crude residue containing **13** was not chromatographed but was directly treated with a catalytic amount of camphorsulfonic acid (CSA) in methylene chloride at 0 °C for a few minutes to afford, after chromatography on silica gel, the 8,13-epoxylabdane **14** (ca. 52% overall yield from **11**) as a single compound as determined by ^{1}H NMR spectroscopy. The triol **14** was easily characterized following interpretation of its spectroscopic data and comparison of these data with those recorded for natural borjatriol and related compounds. Both **14** and borjatriol had similar ^{1}H and ^{13}C NMR parameters except for the differences expected for the change in the 7-hydroxyl group stereochemistry.[17]

In advance of manipulating the hydroxyl group at C-7, triol **14** was converted to hydroxyacetonide **15** by treatment with acetone and anhydrous $CuSO_4$ (90% yield). In practice, the latter step was unnecessary since **15** was more conveniently prepared, without isolation of **14**, by brief treatment of the crude hydroxylation mixture of **11** with CSA in methylene chloride followed by in situ C(14),C-(15)-acetonide formation by the addition of 2,2-dimethoxypropane and stirring at ambient temperature for 1.5 h (53% overall yield from **11**).[18] In addition to the arguments given above supporting the proposed stereochemistry for **14**, the NOE enhancements observed between 8-Me (irradiated) and 10-Me and 13-Me, as well as H-6β and H-7β, gave conclusive evidence of the through-space relation expected for **15** and therefore confirmed beyond doubt the stereochemistry assigned to both **14** and

(14) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765 and literature cited therein.

(15) The 13*S*,14*R* stereochemistry of the major diastereomer **11** was assigned on the basis of the expected reagent-directed epoxidation preference.[16] To check the diastereomeric purity of **11**, a reference sample, which contained a 1:1 mixture of **11** and its 13*R*,14*S* diastereomer **12**, was prepared by the nonasymmetric Sharpless procedure (*t*-BuOOH/VO(acac)$_2$/C$_6$H$_6$/40 °C). Both diastereomeric epoxides were readily distinguished by a separate set of methyl resonances in the 400-MHz ^{1}H NMR spectrum. The upfield methyl resonances for **11** and **12** were at δ 0.75 and 0.74 ppm, respectively. Integration of these signals in the spectrum of **11** obtained from the asymmetric epoxidation showed a diastereoselectivity of ca. 9:1.

(16) Pfenninger, A. *Synthesis* **1986**, 89.

(17) Thus, the H-7 proton appeared in the ^{1}H NMR spectrum of **14** at δ 3.6 ppm as a deformed triplet with an average width ($W_{1/2}$ = 6 Hz) that is only appropriate for an equatorially oriented hydrogen; this indicated the α (axial) orientation of the 7-hydroxyl group. On the other hand, the signals for C-5 and C-9 in the ^{13}C NMR spectrum of **14** (δ 47.32 and 50.25 ppm, respectively) were quite shifted upfield relative to those in borjatriol ($\Delta\delta$ -6.8 and -5.8 ppm) due to the cooperative γ interaction with the 7-OH. The observed downfield shift of C-17 ($\delta_{C\text{-}17}$ 24.43 ppm; $\Delta\delta$ +5.0 ppm) and upfield shift of C-7 ($\delta_{C\text{-}7}$ 73.34 ppm; $\Delta\delta$ -7.2 ppm) in **14** relative to borjatriol were also consistent with the 7α-hydroxy configuration in **14**.

(18) Direct conversion of **13** to **15** was also effected, although in slightly lower yield, by treatment of the crude hydroxylation mixture with acetone and a catalytic amount of CSA at 0 °C for 1 h.

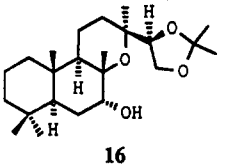
Table I. ^{13}C Chemical Shifts[a] (δ) in ppm from TMS of Compounds 1–18

	1[b]	3	4[b]	5[b,c]	6	8	9	10[b]	11	14	15[d]	16[b]	17[b]	18[b]
C-1	38.85	39.74	39.01	39.32	39.12	39.02	38.93	39.09	39.09	38.73	38.73	38.50	38.98	38.85
C-2	18.49	18.49	18.95	18.15	18.71	18.85	19.40	18.81	18.71	18.51	18.57	18.44	18.28	18.49
C-3	41.90	41.72	41.83	41.79	42.17	42.30	42.15	42.28	42.19	41.97	42.02	41.97	41.65	41.92
C-4	33.31	33.24	33.66	33.17	32.94	32.97	33.60	32.96	32.86	32.73	32.74	32.63	33.75	33.22
C-5	54.19	54.33	54.05	55.82	49.94	50.16	55.51	50.16	50.05	47.32	47.32	47.40	56.67	54.18
C-6	27.52	21.33	23.81	18.15	23.73	23.81	24.46	23.81	23.70	25.45	24.88	24.87	35.80	26.74
C-7	80.58	33.65	42.41	35.68	123.20	122.27	38.34	122.47	122.61	73.34	73.22	72.65	209.16	80.84
C-8	78.31	67.21	211.79	85.80	133.90	135.28	148.46	134.91	134.44	77.16	76.86	*d*	80.76	78.58
C-9	56.06	48.30	62.31	59.88	53.95	55.19	57.11	55.06	55.30	50.25	50.44	46.55	58.95	56.17
C-10	37.02	39.74	42.34	39.09	36.68	36.96	39.76	36.60	36.92	36.68	36.64	36.98	37.01	37.05
C-11	14.19	16.69	20.80	23.43	25.33	25.73	22.31	26.18	22.67	14.10	14.08	13.85	14.28	14.14
C-12	33.62	35.11	17.58	21.34	20.53	35.81	32.72	34.82	35.86	33.44	32.85	29.62	30.45	31.35
C-13	75.57	208.81	84.65	89.43	89.88	160.47	161.03	140.80	61.81	76.35	73.32	73.90	74.92	73.48
C-14	79.23	63.71	68.47	73.16	72.97	115.64	115.60	123.86	64.34	78.69	82.74	81.23	81.87	82.65
C-15	62.93			154.12	154.21	166.62	166.62	59.28	61.27	62.77	64.71	65.32	65.46	65.28
C-16	23.53					25.24	25.32	23.61	22.04	23.53	24.31	24.87	26.02	25.18
C-17	19.41			25.27	22.02	22.15	106.35	22.13	22.20	24.43	24.16	24.97	23.10	19.43
C-18	33.24	33.72	33.45	33.19	33.12	33.16	33.60	33.13	33.08	32.96	32.88	33.08	32.62	33.29
C-19	21.28	21.69	21.65	21.65	21.83	21.87	21.71	21.82	21.76	21.26	21.29	21.42	20.71	21.29
C-20	15.85	16.07	14.85	14.97	13.58	13.50	14.47	13.49	13.52	15.33	15.40	14.44	15.20	15.89
CO_2Me				52.54	52.52	50.80	50.77							
CMe_2											25.14	25.42	24.52	24.87
CMe_2											26.41	26.41	26.02	26.25
CMe_2											109.14	109.38	109.27	109.27

[a] Multiplicities from DEPT experiments. [b] Assignments based on 2D ^1H–^{13}C heterocorrelation experiments. [c] Methyl carbonate carbon signals at 153.84 (OCO_2) and 53.86 (OMe). [d] Due to the low quantity of compound **16** the signal of C-8 was hidden by the solvent signal.

15. It is worthwhile mentioning that acetonide formation of the C(14),C(15)-diol moiety of **14** causes an upfield shift of C-12 of –0.6 ppm and a downfield shift of C-16 of +0.8 ppm. Although smaller than expected, the shifts of C-12 and C-16 when passing from **14** to **15** are in agreement with literature data[5b,19] on related structures and confirmed the stereochemistry at C-14 in both compounds.

In addition to hydroxyacetonide **15**, a small amount of the more polar compound **16**, derived from the minor diastereomeric 13*R*,14*S* epoxide **12**, was obtained from the above reaction. The structure of **16** was supported by



16

strong ^1H and ^{13}C NMR spectral data. As in **15**, the coupling pattern shown by H-7 was consistent only with an α-orientation of the 7-hydroxyl group, which on the basis of a cis course of the osmium tetraoxide dihydroxylation of the C(7)–C(8) double bond also established the stereochemistry at C-8 as depicted in **16**. On the other hand, observation of NOEs between H-14 (irradiated) and both 8-Me and H-11β confirmed that C-14 was β-oriented. Finally, the *S* configuration assigned to C-14 followed from analysis of ^{13}C NMR shift data and comparison with literature data for closely related compounds.[20] The regio- and stereocontrolled (inversion at C-13) formation of **15** and **16** from **11** and **12**, respectively, shows that the pathway reported herein may be used for the preparation of compounds with the 8,13-epoxylabdane or 8,13-epoxy-13-*epi*-labdane skeleton since the stereochemistry at C-13 may be established by the selection of the appropriate DET in the asymmetric epoxidation step.

Transformation of **15** into borjatriol (**1**) required inversion of the axial hydroxyl group at C-7 and removal of the acetonide protective group. The first task was accomplished by oxidation of the hydroxyacetonide **15** with CrO_3 in pyridine at 30 °C for 6–7 days followed by reduction of the resulting ketone **17** with sodium borohydride in ethanol at rt for 1 h.[22] The overall yield of this process was 83%. Finally, cleavage of the acetonide protecting group in **18** using methanol–6 N hydrochloric acid or CSA afforded synthetic borjatriol (**1**), which was spectroscopically and chromatographically identical with natural borjatriol. Thus, the short and enantioselective synthesis of (–)-borjatriol (**1**) starting from the podocarpenone **2**[23] (ca. 15% overall yield) has been realized for the first time through a route that could be used, with appropriate modifications, for other related members of both the 8α,13α- and 8α,13β-epoxylabdane series.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured, respectively, at 200.13 and 50.32 MHz in $CDCl_3$. Mass spectra were obtained at 70 eV for both EI and CI (CH_4 as a reagent gas). Microanalyses were carried out by the Servicio de Microanálisis del CSIC de Barcelona. Analytical TLC was carried out on Merck precoated 0.2-mm thick plates of silica gel 60 HF_{254}. Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230–400 mesh. All reactions involving moisture- or air-sensitive reactants were executed under

(19) (a) Garcia-Alvarez, M. C.; Rodríguez, B.; Garcia-Granados, A.; de Buruaga, A. S. *J. Org. Chem.* **1982**, *47*, 3571. (b) Fernández-Gadea, F.; Rodríguez, B. *J. Org. Chem.* **1984**, *49*, 4721.

(20) Chemical shift values for C-12 (29.62 ppm), C-14 (81.23 ppm), and C-16 (24.87 ppm) are in agreement with the configuration at C-14 given in **16**.[19] Therefore, this compound possesses the antipodal backbone of natural diterpenoid barbatol.[21]

(21) Von Carstenn-Lichterfelde, C.; Rodríguez, B.; Valverde, S. *Experientia* **1975**, *31*, 757.

(22) It is of interest to note that, on the contrary to $NaBH_4$, DIBALH reduced **17** to the axial alcohol **15** (DIBALH (2 equiv), THF, –78 °C; 80% yield); apparently, the factors related to steric control are prevailing in this case.

(23) Since several total syntheses of podocarpenone **2** have already been described[24] the synthesis described in the present work represents a formal total synthesis of borjatriol. It also confirms the absolute stereochemistry of borjatriol as given in **1**, which had been proposed on the basis of chemical correlation and by the application of Horeau's method for the determination of the configuration at C-14.[1]

(24) ApSimon, J. W.; Fyfe, K. E.; Greaves, A. M. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1984; Vol. 6, pp 85–139.

an atmosphere of dry argon or nitrogen using oven-dried or flame-dried glassware and freshly distilled and dried solvents. Unless stated otherwise, reaction mixtures were worked up by addition of water and extraction with ether, the ethereal extract being washed with water and brine and dried using anhyd sodium sulfate. Evaporation was performed under reduced pressure. Basic workup included a saturated aqueous wash after ether extraction. ^{13}C NMR chemical shift data are collected in Table I.

(+)-8α,14-Epoxypodocarpan-13-one (3). To a solution of enone **2** (1.5 g; 6.09 mmol) in MeOH (74 mL) were added 30% H_2O_2 (3.65 mL) and 10% aqueous NaOH solution (3.65 mL) at 0 °C. The reaction mixture was stirred for 12 h at the same temperature. After aqueous workup, a solid was obtained that could be used without further purification for the next step or chromatographed (hexane–ethyl acetate (9:1) as eluent) to give epoxide **3** (1.47 mg, 92%) as a white solid: mp 106–106.5 °C (from pentane) (lit.[7] 102–103 °C); $[\alpha]^{22}_D$ +55° (*c* 2, $CHCl_3$); IR (KBr) 1700, 1260, 800 cm^{-1}; ^1H NMR δ 3.13 (s, 1 H, H-14), 0.89 (s, 3 H, 4α-Me), 0.82 (s, 3 H, 4β-Me), 0.79 ppm (s, 3 H, 10-Me); MS *m/e* (relative intensity) 262 (M^+, 14), 247 (15), 206 (11), 137 (75), 123 (74), 41 (100). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found C, 77.87; H, 10.07.

(−)-15,16,17-Trinorlabd-13-yn-8-one (4). To a suspension of silica gel (1.32 g; activated at 300 °C overnight) in anhyd CH_2Cl_2 (13 mL) was added a solution of epoxy ketone **3** (1.350 g, 5.1 mmol) and *p*-toluenesulfonohydrazide (950 mg, 5.1 mmol) in CH_2Cl_2 (13 mL) at −20 °C. After being stirred at this temperature for 12 h, the resulting mixture was warmed to rt and stirring was continued for 4 h. The reddish solution was then filtered to remove the silica gel, which was washed with CH_2Cl_2. The filtrate and washing were combined and evaporated to yield a crude product which was chromatographed (hexane–ether (98:2) as eluent) to give ynone **4** (1.254 g, 82%) as a colorless oil which crystallized on standing: mp 38–39 °C (from pentane) (lit.[7] an oil); $[\alpha]^{20}_D$ −26° (*c* 0.7, $CHCl_3$); IR (KBr) 3300, 1715, 1200, 980 cm^{-1}; ^1H NMR δ 0.94 (s, 3 H, 4α-Me), 0.82 (s, 3 H, 4β-Me), 0.69 ppm (s, 3 H, 10-Me); MS *m/e* (relative intensity) 246 (M^+, 3), 231 (4), 218 (1), 83 (100). Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found C, 82.86; H, 10.88.

(+)-Methyl 8β-[(Methoxycarbonyl)oxy]-16-norlabd-13-yn-15-oate (5). To a solution of acetylenic ketone **4** (1.0 g, 4 mmol) in anhyd THF (20 mL) was added a solution of MeLi (1.5 M ethereal solution, 5.5 mL, 8.2 mmol) at −78 °C, and the mixture was stirred for 1.5 h at this temperature. Anhyd HMPA (1.5 mL) was added followed by excess methyl cyanoformate (1.3 mL, 16 mmol). After being stirred for 2 h at −78 °C, the mixture was quenched by the addition of saturated aqueous NH_4Cl and subjected to aqueous workup to give an oil. Chromatography (hexane–ethyl acetate (98:2) as eluent) gave **5** (1.23 g, 80%) as an oil: $[\alpha]^{20}_D$ +41° (*c* 0.9, $CHCl_3$); IR (film) 2240, 1740, 1720, 1250 cm^{-1}; ^1H NMR δ 3.73 (s, 3 H, CO_2Me), 3.66 (s, 3 H, OCO_2Me), 2.85 (m, 1 H, H-7β), 2.33 (m, 2 H, H-12), 1.48 (s, 3 H, 8-Me), 0.90 (s, 3 H, 10-Me), 0.84 (s, 3 H, 4α-Me), 0.79 ppm (s, 3 H, 4β-Me); MS *m/e* (relative intensity) 363 (M^+ − 15, 0.5), 303 (1), 287 (3), 59 (100). Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found, C, 69.78; H, 9.13.

(+)-Methyl 16-Norlabd-7-en-13-yn-15-oate (6). A mixture of carbonate **5** (1.1 g, 2.9 mmol) and powdered Pyrex glass (2.5 g) was heated (Kugelrohr) for 30 min at 210 °C and 100 mmHg. The residue was dissolved in CH_2Cl_2 and filtered. The brownish oil obtained after evaporation of the solvent was chromatographed (hexane–ethyl acetate (9:1) as eluent) to give a 5:1 mixture (by ^1H NMR and GC ($^1/_8$-in. diameter, 2-m column packed with 5% EGA on Chromosorb W AW; 250 °C injector and detector temperature, 210 °C column temperature)) of the $\Delta^{7,8}$ olefin **6** and its $\Delta^{8,17}$ isomer **7** (808 mg, 92%) as an oil. Chromatography of this mixture on 25% $AgNO_3$–silica gel (hexane–ethyl acetate (95:5) as eluent) afforded only **6** and a mixture of very polar compounds. Compound **6**: an oil; $[\alpha]^{20}_D$ +27° (*c* 2.4, $CHCl_3$); IR (film) 3020, 2230, 1710, 1250, 1070, 810, 750 cm^{-1}; ^1H NMR δ 5.4 (m, 1 H, H-7), 3.74 (s, 3 H, CO_2Me), 2.49 (ddd, *J* = 17.2, 14.5 and 9.3 Hz, 1 H, H-12), 2.3 (ddd, *J* = 17.2, 8.3 and 7.9 Hz, 1 H, H-12′), 1.65 (br s, 3 H, 8-Me), 0.85 (s, 3 H, 4β-Me), 0.83 (s, 3 H, 4α-Me), 0.73 ppm (s, 3 H, 10-Me); MS *m/e* (relative intensity) 302 (M^+, 3), 287 (5), 272 (7), 243 (2), 191 (3), 178 (14), 124 (40), 109 (100). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 9.98. Found C, 79.90; H, 10.04.

(−)-Methyl (*Z*)-Labda-7,13-dien-15-oate (8). (a) From Pure 6. To CuI (63 mg, 0.33 mmol) suspended in dry THF (1 mL) at −20 °C under oxygen-free N_2[25] was added 0.387 mL (0.62 mmol) of a 1.6 M solution of MeLi in ether. The mixture was allowed to reach −5 °C, and then it was cooled to −78 °C and a solution of **6** (95 mg, 0.31 mmol) in dry THF (1 mL), also cooled to −78 °C, was added dropwise. After 2 h, 0.7 mL of precooled MeOH (−78 °C) were added dropwise followed by saturated aqueous NH_4Cl. Usual workup afforded an oil, which after chromatography (hexane–ether (9:1) as eluent) gave the α,β-unsaturated ester **8** (96 mg, 96%) as a colorless oil: $[\alpha]^{23}_D$ −13° (*c* 6.2, $CHCl_3$); IR (film) 3040–2800, 1720, 1650, 1160, 850 cm^{-1}; ^1H NMR δ 5.61 (br s, 1 H, H-14), 5.38 (m, 1 H, H-7), 3.65 (s, 3 H, CO_2Me), 2.67 (m, 2 H, H-12), 1.88 (d, *J* = 1.1 Hz, 3 H, 13-Me), 1.76 (br s, 3 H, 8-Me), 0.85 (s, 3 H, 4β-Me), 0.83 (s, 3 H, 4α-Me), 0.73 ppm (s, 3 H, 10-Me); MS *m/e* (relative intensity) 318 (M^+, 5), 303 (4), 205 (49), 191 (11), 135 (29), 114 (100). Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.50; H, 10.99.

(b) From the Mixture of 6 and 7. As above using a 5:1 mixture of olefins **6** and **7** (700 mg). Chromatography on 15% $AgNO_3$–silica gel (hexane–ether (97:3) as eluent) afforded **8** (595 mg, 79%) and the exocyclic isomer **9** (110 mg, 15%) also as an oil: $[\alpha]^{23}_D$ +1.4° (*c* 11.2, $CHCl_3$); IR (film) 3060, 1710, 1690, 1630, 1160, 875, 840 cm^{-1}; ^1H NMR δ 5.5 (br s, 1 H, H-14), 4.64 and 4.85 (each br s, 1 H each, H-17), 3.65 (s, 3 H, CO_2Me), 2.53 (dd, *J* = 8.3 and 7.3 Hz, 2 H, H-12), 2.36 (ddd, *J* = 12.7, 4.1, and 2.45 Hz, 1 H, H-7β), 1.87 (d, *J* = 1 Hz, 3 H, 13-Me), 0.85 (s, 3 H, 4α-Me), 0.78 (s, 3 H, 4β-Me), 0.65 ppm (s, 3 H, 10-Me); MS *m/e* (relative intensity) 318 (M^+, 6), 303 (22), 177 (17), 137 (15), 113 (76), 41 (100).

(−)-(*Z*)-Labda-7,13-dien-15-ol (10). To a solution of α,β-unsaturated ester **8** (500 mg, 1.57 mmol) in anhyd ethyl ether (31 mL), cooled at −78 °C, was added DIBALH (1 M in cyclohexane, 3.9 mL, 3.9 mmol) over 2 min. The resulting mixture was allowed to stir for 30 min at −78 °C and then was carefully quenched with diluted hydrochloric acid. Basic workup afforded the crude allylic alcohol that was purified by chromatography (hexane–ethyl acetate (9:1) as eluent) to give pure **10** (442 mg, 97%) as a colorless oil: $[\alpha]^{23}_D$ −3.6° (*c* 17.3, $CHCl_3$); IR (film) 3600–3100, 3020–2840, 1450, 1380, 1000 cm^{-1}; ^1H NMR δ 5.87 (m, 2 H, H-7 and H-14), 4.1 (d, *J* = 7.4 Hz, 2 H, H-15), 2.21 (dt, *J* = 12.8 and 5.5 Hz, 1 H, H-12), 2.1–1.8 (m, 3 H, H-12, H-6 and H-1β), 1.75 (br s, 3 H, 8-Me), 1.7 (d, *J* = 1 Hz, 3 H, 13-Me), 0.85 (s, 3 H, 4β-Me), 0.83 (s, 3 H, 4α-Me), 0.72 ppm (s, 3 H, 10-Me); MS *m/e* (relative intensity) 290 (M^+, 1), 275 (0.9), 204 (100), 71 (14).

(13*S*,14*R*)-Epoxylabd-7-en-15-ol (11). With stirring, freshly distilled titanium(IV) isopropoxide (0.164 mL, 0.55 mmol) and (−)-diethyl tartrate (170 mg, 0.82 mmol) were added sucessively to a suspension of 4-Å powdered, activated molecular sieves (550 mg) in dry CH_2Cl_2 (6 mL) at −30 °C. After 10 min at −20 °C, dry *tert*-butyl hydroperoxide (3 M solution in isooctane, 0.69 mL, 2.1 mmol) was added and the mixture was stirred at this temperature for 45 min. Then a solution of the allylic alcohol **10** (400 mg, 1.37 mmol) in dry CH_2Cl_2 (6 mL), previously stirred with 4-Å activated, powdered molecular sieves for 15 min, was transferred via cannula to the reaction flask maintaining the reaction temperature between −25 and −30 °C. After being stirred at this temperature for 2 h, the reaction was quenched by pouring into a mixture of ether (70 mL) and saturated Na_2SO_4 (aq) (1.5 mL). After being stirred for 30 min the mixture was filtered through silica gel and rinsed through with ether. The combined filtrates were concentrated under vacuum and the residue was purified by chromatography (hexane–ethyl acetate (3:1) as eluent) to give a 9:1 mixture (by ^1H NMR, see ref 15) of epoxy alcohol **11** and its 13*R*,14*S* diastereomer **12** (390 mg, 93%) as an oil: IR (film) 3650–3100, 3020, 1450, 1380, 1030, 850 cm^{-1}; ^1H NMR (only signals of the major epoxide are given) δ 5.35 (br s, 1 H, H-7), 3.82 (dd, *J* = 12.3 and 4.3 Hz, 1 H, H-15), 3.63 (dd, *J* = 12.3 and 6.6 Hz, 1 H, H-15′), 2.94 (dd, *J* = 6.6 and 4.3 Hz, 1 H, H-14), 1.62 (br s, 3 H, 8-Me), 1.32 (s, 3 H, 13-Me), 0.84 (s, 3 H, 4β-Me), 0.81 (s, 3 H, 4α-Me), 0.73 (s, 3 H, 10-Me); MS *m/e* (relative intensity) 306 (M^+, 0.1), 288 (0.1), 275 (0.5), 231 (2), 204 (100), 205 (15), 191 (4).

(25) Kauffmann, G. B.; Pinnell, R. P. *Inor. Synth.* **1960**, 3.

(−)-(14*R*)-8,13-Epoxy-14,15-(isopropylidenedioxy)labdan-7α-ol (15). (a) Stepwise Procedure. To a solution of the above prepared epoxy alcohol **11** (70 mg, 0.23 mmol) in pyridine (0.5 mL) was added dropwise with stirring at 0 °C a solution of OsO_4 (62.2 mg, 0.25 mmol) in pyridine (0.5 mL). The mixture was stirred at rt overnight and then treated with a solution of $NaHSO_3$ (101 mg, 0.97 mmol) in water (1.8 mL) and pyridine (1.2 mL). The reaction mixture was vigorously stirred at rt for 2 h and then worked up.

A solution of the mixture obtained above containing the epoxy triol **13** (77 mg) and a catalytic amount of CSA (2.8 mg, 0.01 mmol) in dry CH_2Cl_2 (1.9 mL) was stirred at 0 °C for 15 min an then allowed to warm to rt. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and then worked up as usual. Chromatography of the crude product (CH_2Cl_2–acetone (3:2) as eluent) afforded (14*R*)-8,13-epoxylabdane-7α,14,15-triol (**14**) (40.4 mg, 52%) as a semisolid: $[\alpha]^{21}_D$ −21.4° (*c* 0.21, $CHCl_3$); IR (film) 3600–3100, 1460, 1380, 1120 cm^{-1}; ^1H NMR ($CDCl_3$–D_2O) δ 3.7 (m, 2 H, H-15), 3.6 (deformed t, $W_{1/2}$ = 6 Hz, 1 H, H-7β), 3.5 (dd, *J* = 6.1 and 3.7 Hz, 1 H, H-14), 1.26 (s, 3 H, 8-Me) 1.21 (s, 3 H, 13-Me), 0.84 (s, 3 H, 4α-Me), 0.76 (s, 3 H, 4β-Me), 0.75 ppm (s, 3 H, 10-Me); MS (CI) *m/e* (relative intensity) 341 (M^+ + 1, 24), 323 (57), 305 (100), 279 (23).

The triol **14** (35 mg, 0.10 mmol) was dissolved in anhyd acetone (14 mL), and $CuSO_4$ (210 mg, 1.3 mmol) was added to the solution. The stirred mixture was refluxed for 48 h and worked up as usual. Chromatography of the crude product (hexane–ethyl acetate (9:1) as eluent) afforded alcohol **15** (35.5 mg, 91%) as a white solid: mp 114–115 °C (from MeOH); $[\alpha]^{20}_D$ −2.9° (*c* 1.8, $CHCl_3$); IR (KBr) 3560, 1380, 1375, 1210, 1070, 1040, 850 cm^{-1}; ^1H NMR δ 3.92–3.7 (m, 3 H, H-14 and H-15), 3.57 (m, $W_{1/2}$ = 6.6 Hz, 1 H, H-7β), 1.39 and 1.31 (each s, 3 H each, Me_2C), 1.25 (s, 3 H, 8-Me), 1.18 (s, 3 H, 13-Me), 0.84 (s, 3 H, 4α-Me), 0.76 (s, 3 H, 4β-Me), 0.75 ppm (s, 3 H, 10-Me); MS *m/e* (relative intensity) 365 (M^+ − 15, 4), 279 (79), 261 (36), 243 (22), 203 (12), 43 (100). Anal. Calcd for $C_{20}H_{40}O_4$: C, 72.59; H, 10.59. Found: C, 72.20; H, 10.60.

(b) In Situ C(14),C(15)-Acetonide Formation. In the same manner to that described for the stepwise procedure, **11** (175 mg, 0.57 mmol) was treated with OsO_4 (155 mg, 0.62 mmol) and $NaHSO_3$ (253 mg, 2.42 mmol). After treatment of the crude hydroxylation product with CSA (7 mg, 0.028 mmol) in anhyd CH_2Cl_2 (4.5 mL), the reaction was quenched with 2,2-dimethoxypropane (4.5 mL) and the resulting mixture was stirred for rt for 1.5 h. The mixture was poured into saturated aqueous $NaHCO_3$ and worked up as usual to afford an oil which was purified by chromatography (hexane–ethyl acetate (9:1) as eluent) to give **15** (113 mg, 53% from **11**). Further elution with the same eluent afforded **16** (9.8 mg, 4.5%) also as an oil: $[\alpha]^{22}_D$ −2.3° (*c* 0.8, $CHCl_3$); IR (film) 3650–3100, 1250, 1080, 850 cm^{-1}; ^1H NMR δ 4.07 (dd, *J* = 7.6 and 6.8 Hz, 1 H, H-14), 3.91 (dd, *J* = 7.9 and 6.8 Hz, 1 H, H-15), 3.73 (dd, *J* = 7.9 and 7.8 Hz, 1 H, H-15′), 3.55 (m, $W_{1/2}$ = 6 Hz, 1 H, H-7β), 1.40 and 1.34 (each s, 3 H each, Me_2C), 1.25 (s, 3 H, 8-Me), 1.18 (s, 3 H, 13-Me), 0.85 (s, 3 H, 4α-Me), 0.77 ppm (s, 6 H, 4β-Me and 10-Me); MS (CI) *m/e* (relative intensity) 381 (M^+ + 1, 19), 380 (M^+, 8), 365 (24), 363 (83), 347 (34), 305 (99), 279 (26), 83 (100).

(−)-(14*R*)-8,13-Epoxy-14,15-(isopropylidenedioxy)labdan-7-one (17). To a solution of alcohol **15** (101 mg, 26.3 mmol) in pyridine (6.5 mL) was added CrO_3 (315 mg, 3.2 mmol) in small portions, and the solution was stirred for a week at 30 °C. The mixture was treated with 2-propanol (3 mL) and then stirred for an additional 1 h at rt. Aqueous workup followed by chromatography (hexane–ethyl acetate (75:25) as eluent) gave ketone **17** (96 mg, 96%) as a solid: mp 181–182 °C (from hexane) (lit.[1,2] mp 179–181 °C); $[\alpha]^{20}_D$ −29.3° (*c* 1.3, $CHCl_3$); IR (KBr) 1725, 1210, 1130, 1070, 1060, 860 cm^{-1}; ^1H NMR δ 4.1–3.9 (m, 3 H, H-14 and H-15), 2.54 (t, *J* = 14 Hz, 1 H, H-6β), 2.34 (dd, *J* = 14 and 3 Hz, 1 H, H-6α), 1.46 (s, 3 H, 8-Me), 1.37 and 1.29 (each s, 3 H each, Me_2C), 1.32 (s, 3 H, 13-Me), 0.96 (s, 3 H, 10-Me), 0.82 (s, 3 H, 4α-Me), 0.81 ppm (s, 3 H, 4β-Me); MS *m/e* (relative intensity) 363 (M^+ − 15, 3), 277 (100), 139 (16), 123 (63).

(+)-(14*R*)-8,13-Epoxy-14,15-(isopropylidenedioxy)labdan-7β-ol (18). $NaBH_4$ (13.6 mg, 0.36 mmol) was added to a stirred solution of the ketone **17** (90 mg, 0.24 mmol) in ethanol (9.5 mL) at rt, and the mixture was then stirred at the same temperature for 1 h. Acetone (7 mL) was then added, and the mixture was stirred for a further 10 min and worked up. Chromatography (hexane–ethyl acetate (8:2) as eluent) afforded the alcohol **18** (76.5 mg, 87%) as a solid: mp 161–162 °C (from pentane) (lit.[1,2] mp 161–162 °C); $[\alpha]^{22}_D$ +7° (*c* 3.2, $CHCl_3$); IR (KBr) 3580, 1215, 1060, 860 cm^{-1}; ^1H NMR δ 3.91–3.84 (m, 3 H, H-14 and H-15), 3.46 (dd, *J* = 11.4 and 4.5 Hz, 1 H, H-7α), 1.8 (ddd, *J* = 13, 4.5 and 2.3 Hz, 1 H, H-6α), 1.37 and 1.31 (each s, 3 H each, Me_2C), 1.23 (s, 3 H, 13-Me), 1.22 (s, 3 H, 8-Me), 0.85 (s, 3 H, 4α-Me), 0.78 (s, 3 H, 4β-Me), 0.75 ppm (s, 3 H, 10-Me); MS *m/e* (relative intensity) 380 (M^+, 3), 365 (20), 305 (100), 279 (56), 264 (14). Anal. Calcd for $C_{23}H_{40}O_4$: C, 72.59; H, 10.59. Found C, 72.57; H, 10.64.

(−)-(14*R*)-8,13-Epoxylabdane-7β,14,15-triol (Borjatriol, 1). A solution of the above prepared alcohol (75 mg, 0.2 mmol) and a catalytic amount of CSA (14 mg; 0.06 mmol) in MeOH (9 mL) was stirred at rt for 3 h. Basic workup, using ethyl acetate to extract, followed by chromatography (CH_2Cl_2–acetone (3:2) as eluent) gave borjatriol (66 mg, 98%) as an amorphous solid: $[\alpha]^{22}_D$ −1.1° (*c* 0.7, $CHCl_3$) (lit.[1,2] $[\alpha]^{22}_D$ −2.3°) [its triacetate: mp 123–124 °C (from EtOH–H_2O) (lit.[1,2] mp 121.5–122.5 °C); $[\alpha]^{22}_D$ +49.3° (*c* 2.8 $CHCl_3$) (lit.[1] $[\alpha]^{22}_D$ +50.4°)]; IR (KBr) 3600–3100, 1460, 1390, 1120, 1070, 1000 cm^{-1}; ^1H NMR δ ($CDCl_3$–D_2O) 3.63 (m, 2 H, H-15), 3.5 (dd, *J* = 11.3 and 4.5 Hz, 1 H, H-7α), 3.23 (dd, *J* = 5.7 and 4.1 Hz, 1 H, H-14), 1.8 (ddd, *J* = 13, 4.5, 2.3 Hz, 1 H, H-6α), 1.25 (s, 3 H, 8-Me), 1.20 (s, 3 H, 13-Me), 0.84 (s, 3 H, 4α-Me), 0.77 (s, 3 H, 4β-Me), 0.74 ppm (s, 3 H, 10-Me); MS *m/e* (relative intensity) 325 (M^+ − 15, 0.3), 279 (46), 261 (18), 243 (14), 43 (100).

Acknowledgment. Financial support from CAICYT (Grant No PB89-0528) is gratefully acknowledged. We also thank Dr. D. Craig for manuscript revision and Dr. M. J. Alcaraz, for an authentic sample of borjatriol. One of us (A.C.C.) thanks the Caja de Ahorros de Valencia for a predoctoral scholarship.