Epoxidation Studies on Lathyra-6(17),12-dienes − Revised Structure of the *Euphorbia* Factor L_1

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As part of an investigation aimed at mimicking certain steps of the biogenesis of the polycyclic *Euphorbia* diterpenoids from macrocyclic precursors, the epoxidation of lathyrol and its esters with (peroxy/peroxo)metal complexes and non-metal (peracids and dioxiranes) oxidants was investigated. Treatment of lathyrol esters with methyl(trifluoromethyl)-dioxirane gave 6(17)β-epoxides as the only reaction products in very high yield. Conversely, lathyrol itself proved amenable to epoxidation only with the TBHP–$VO(acac)_2$ protocol. Surprisingly, the reaction was not chemoselective, and also the enone double bond was epoxidized, eventually affording a rearranged compound of the 14(13→12)-*abeo*-lathyrane type. Based on the stereochemical course of the epoxidation of lathyrol esters and on NMR experiments on the natural product, the configuration at C-6 of the *Euphorbia* Factor L_1 was revised, overturning a thirty-year misconception on the structure of this compound.

Introduction

Over the past few decades, a significant amount of research has been dedicated to elucidate the molecular and cellular mechanisms of activity of phorboids,[1] a class of diterpenes exemplified by the three basic polyols phorbol (**1**), ingenol (**2**), and resiniferonol (**3**), and typical of plants from the *Euphorbiaceae* and *Thymelaeaceae* families (Scheme 1). Despite this intense activity, the biogenesis of phorboids has remained a virtually unexplored area of investigation. Topology considerations and data of co-occurrence suggest that the transannular cyclisation of a lathyrane precursor is a key step en route to the tigliane skeleton of phorbol, providing the C-8 to C-14 link (lathyrane numbering). However, the functionalisation of natural lathyranes, and especially the lack of substituents at C-8 in lathyrol derivatives, give no clue to the mechanistic details underlying this reaction.[2]

Macrocyclic lathyranes have a pre-eminent role also in the biogenesis of other types of *Euphorbia* diterpenoids,[1b] and the study of these relationships and their chemical mimics could provide a starting conceptual framework to study the biogenesis of phorboids. In this context, one of the most elementary processes is the epoxylathyrane (**4**) to premyrsinane (**5**) conversion through an *exo-tet* intramolecular cyclisation (Scheme 2). The co-occurrence of lathyranes and premyrsinanes with a similar functionalisation pattern backs up this hypothesis,[3] but so far no attempt has been made to mimic this transformation under laboratory conditions.

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Several lathyradienes have been described,[1] but only one epoxide of the 6(17)-type is known, the so-called *Euphorbia* Factor L_1 (**6a**).[4] This compound holds a venerable position in natural product chemistry, being the first *Euphorbia* diterpenoid obtained in pure form.[5] It was originally considered a steroid and named euphorbiasterone, but later studies revealed its diterpenoid nature,[4] with the final configurational details eventually disclosed by an X-ray analysis.[6] The *Euphorbia* factor L_1 is easily obtained in multigram amounts and without chromatography from the seeds of the caper spurge (*Euphorbia lathyris* L.), an agricultural commodity.[7a] Though the epoxide ring of the *Euphorbia* factor L_1 has a configuration opposite to that requested to test the lathyrane-premyrsinane relationship, a deoxygenation-epoxidation protocol is expected to remodel this easily available compound, providing the epimeric epoxide **8b**, a suitable candidate for biomimetic transannular cyclizations (Scheme 3). Lathyrol esters like **7b**, the deoxygenation product of **6a**, in fact adopt a conformation with the exocyclic double bond almost perpendicular to the mean plane of the macrocycle, and oriented toward its α-face.[3] The principle of peripheral attack dictates that epoxidation of these compounds should exclusively afford epoxides with the requested β-configuration.[8] The study of the epoxidation of lathyrol esters and lathyrol itself became the target of this investigation, which disclosed some unexpected chemistry and eventually led to the structural revision of the *Euphorbia* factor L_1.

The *Euphorbia* factor L_3 (**7a**)[7,9] was used to explore the reactivity of lathyrol esters in epoxidation reactions. Among the reagents considered, methyl(trifluoromethyl)dioxirane (TFD) gave the best results in terms of conversion and selectivity, leading to the quantitative formation of the epoxide **8a** (Scheme 4). Dimethyldioxirane (DMD) and peracids [*meta*-chloroperoxybenzoic acid (MCPBA), magnesium monoperoxyphthalate] gave an incomplete conversion, even

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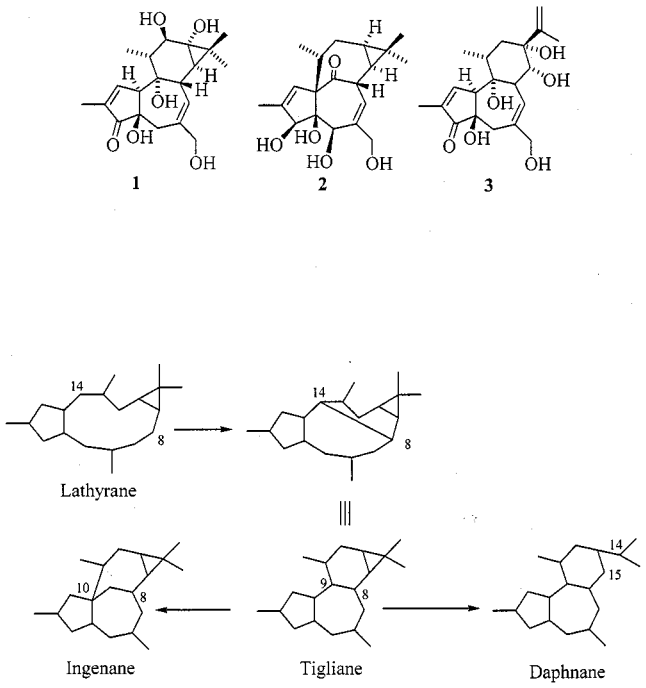
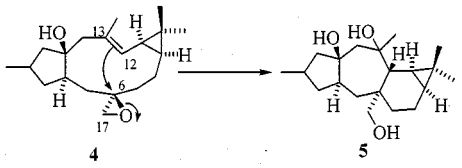
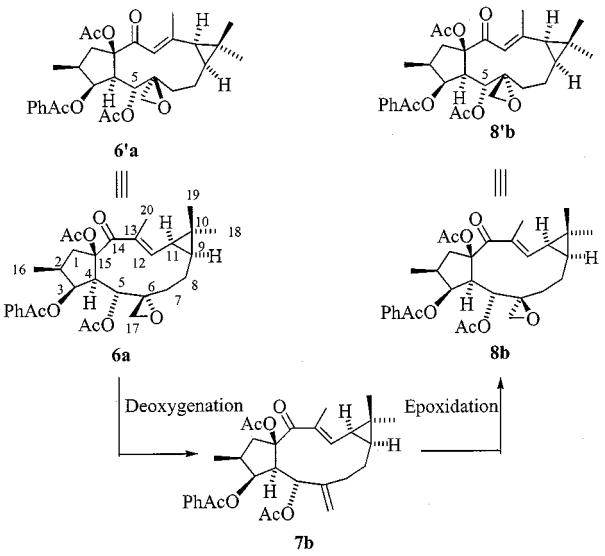


Scheme 1. Biogenetic relationships between phorboids and lathyrane diterpenoids

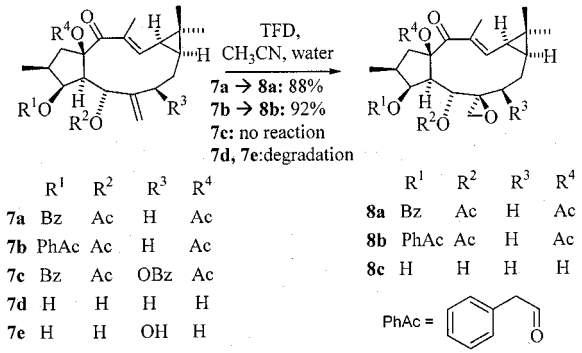


Scheme 2. Transannular cyclization of $\Delta^{6(17),12}$-lathyradiene 6β,17-epoxides (**4**) to premyrsinanes (**5**)



Scheme 3. Two-dimensional representation of the *Euphorbia* factor L_1, its epimer at C-6, and their possible interconversion (correct structure for the natural product = **8b** and **8′b**)

with a large excess of the oxidant, while with methyltrioxorhenium/urea–hydrogen peroxide and Oxone no reaction occurred. In small-scale experiments (0.1 mmol of olefin substrate), no difference was observed between TFD isolated or generated in situ.[10] The latter protocol was therefore used throughout. The β-configuration of the epoxide was expected from previous investigations on the conformation of lathyrol esters in solution and in the solid state,[3] and was confirmed by the detection of diagnostic NOE correlations between the geminal epoxide protons (17a-H, 17b-H) and the α-oriented protons at the ring junctions (4-H, 9-H, 11-H).



	R^1	R^2	R^3	R^4
7a	Bz	Ac	H	Ac
7b	PhAc	Ac	H	Ac
7c	Bz	Ac	OBz	Ac
7d	H	H	H	H
7e	H	H	OH	H

	R^1	R^2	R^3	R^4
8a	Bz	Ac	H	Ac
8b	PhAc	Ac	H	Ac
8c	H	H	H	H

Scheme 4. Epoxidation of lathyrol esters

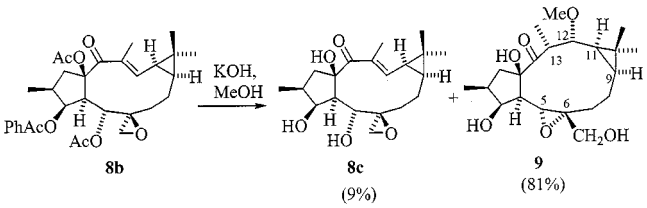
This epoxidation protocol was then applied to the deoxy-*Euphorbia* factor L_1 (**7b**), a compound easily prepared in multigram amounts by treatment of the natural product with iodine and triphenylphosphane.[3] Surprisingly, an epoxide identical to the *Euphorbia* factor L_1 was obtained. The β-orientation of the epoxide was evident from the observation of the same set of NOE effects evidenced in the epoxidation product of **7a**. The structure of the *Euphorbia* Factor L_1 should therefore be re-formulated as **8b**, a revision which places this compound on the mainstream of the

biogenetic route to premyrsinanes and other lathyrane-derived *Euphorbia* skeleta. The configuration at C-6 of all compounds obtained from the acid-induced cyclisation of the *Euphorbia* factor L_1 should also be revised.[11]

The structure of the *Euphorbia* factor L_1 was based on an X-ray study,[6] but the claimed configuration at C-5 was later proven to be incorrect,[12] and details of the diffractometric analysis were never published nor deposited at the Cambridge Data Base. The X-ray generated drawing provided in the original publication also gives no clue also with regard to the orientation of the epoxide oxygen atom. In the original report, the structure of the *Euphorbia* factor L_1 is drawn in such a way that C-6 is a re-entrant angle (**8′b** after correction of the original configuration at C-5) (Scheme 3).[6] Re-entrant and vertex angles are related by a C_2 rotation along an axis passing through the C-(n − 1) and C-(n + 1) atoms. This reverts the meaning of the thickened and broken lines used to locate substituents, whose actual orientation is the opposite of what intuitively expected.[13] The configuration at C-6 of the *Euphorbia* factor L_1 was therefore correctly represented in the original publication (formula **8′b**, broken line at a re-entrant angle, meaning a β-orientation, for the epoxide oxygen atom), with troubles arising only in the subsequent publications by the same group who reported the structure of the *Euphorbia* factor L_1, where a more expanded representation of the lathyrane skeleton with C-6 as a vertex angle was employed (**6a**).[9] Since the configuration symbol for the oxygen atom at C-6 was not changed from a broken to a thickened line, formulae **6a** and **8′b** actually represents C-6 epimeric compounds.[9] The representation **6a** served as a base for all subsequent studies on this type of compounds, and was also employed by *Chemical Abstracts* to assign the configuration of epoxylathyrol and its derivatives.[14]

The 7-hydroxylathyrol ester *Euphorbia* factor L_2 (**7c**)[15] could not be epoxidized, and was recovered unchanged after treatment with TFD, DMD, and MCPBA. A possible explanation for the lack of reactivity of **7c** is that the introduction a β-oxygen function on the allylic carbon atom C-7 is detrimental from the electronic point of view (further deactivation of the exomethylene group toward attack by electrophilic reagents) and/or from the steric point of view (shielding of the external β-face of the exomethylene group).

"Unnatural" α-epoxides could in principle be available from lathyrol (**7d**), since this compound adopts a conformation with the exomethylene on the mean plane of the macrocycle,[3] and attack from both faces of the olefin bond is therefore possible. To test this possibility, lathyrol (**7d**), and hydroxylathyrol (**7e**) were prepared by hydrolysis (KOH, MeOH) of the *Euphorbia* Factor L_3 (**7b**) and L_2 (**7c**), respectively. Epoxylathyrol (**8c**) was similarly prepared from the *Euphorbia* factor L_1 to serve as a reference epoxide (Scheme 5). While the hydrolysis of the *Euphorbia* factors L_3 and L_2 afforded the parent polyols as the only reaction product, that of the *Euphorbia* factor L_1 gave instead the Payne-rearranged Michael adduct **9** as the major reaction product (81%), and only a modest yield (9%) of epoxylathyrol (**8c**). The involvement of the oxygen function at C-5 in an epoxide ring was evident from the value of the one-bond C−H coupling between C-5 and H-5 (173 Hz), typical of a three-membered ring.[16] The α-orientation of the 12-methoxy and the 13-methyl groups was in accordance with NOESY experiments, which disclosed a correlation between these groups and the cyclopropane protons (9-H and 11-H). Since the formation of Michael adducts was not observed during the hydrolysis of lathyrol esters, Payne rearrangement seemingly causes subtle stereoelectronic effects which increase the reactivity of the endocyclic enone system toward nucleophiles.

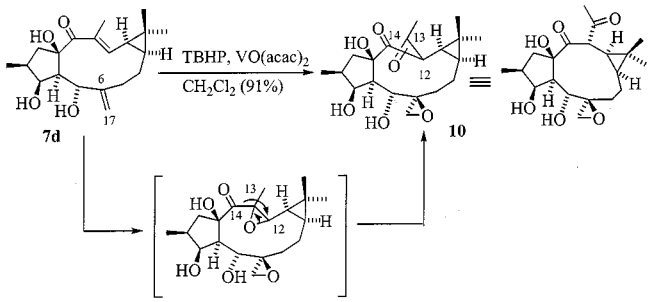


8b **8c** (9%) **9** (81%)

Scheme 5. Hydrolysis of the *Euphorbia* factor L_1 (**8b**)

The epoxidation of lathyrol (**7d**) and hydroxylathyrol (**7e**) with dioxiranes, peracids, and methyltrioxorhenium/urea−hydrogen peroxide gave complex mixtures of degraded compounds, from which no pure product could be obtained. This also occurred when the reaction was carried out at low temperature (−15 °C) and an excess of the oxidant was avoided. However, lathyrol (but not epoxylathyrol) proved amenable to epoxidation with the *tert*-butyl hydroperoxide (TBHP)−$VO(acac)_2$ system.[17] Surprisingly, the ring-contracted 14(13→12)-*abeo*-lathyrane epoxide **10** was obtained as the only reaction product (91% yield) (Scheme 6). HRMS showed the introduction of two oxygens atoms, while the NMR spectra of **10** showed the lack of unsaturations, with the *exo*-methylene frequencies replaced by those of a spiro-epoxide, and the signals of the endocyclic double bond replaced by those of one carbonyl (δ = 205.3, s) and a non-oxygenated deshielded methine group (δ_H = 4.37, d; δ_C = 56.2, d). The latter was coupled to the cyclopropane proton 11-H ($J_{11,12}$ = 11.8 Hz), and showed HMBC correlations with two carbonyl groups. These observations were diagnostic of a ring-contracted structure, with extrusion of C-13 from the macrocycle. NOESY experiments revealed that the 6(17)-epoxide oxygen atom was β-oriented (correlations of the epoxide protons with 5-H, 9-H and 11-H), and that the acetyl group was α-oriented (correlation 20-H, 9-H and 20-H, 11-H).

Compound **10** is presumably derived from the pinacol-type rearrangement of a 6(17),12-bis(epoxide), as depicted in the Scheme 6. This mechanism, though credible in retrospect, was totally unexpected, since the epoxidation of an enone double bond with the TBHP−$VO(acac)_2$ system is, to the best of our knowledge, unprecedented. When substoichiometric amounts of TBHP were employed, a mixture of **10** and unchanged lathyrol (**7d**) was obtained. Therefore, the two double bonds of lathyrol react at a comparable rate, a surprising observation on account of their different elec-



Scheme 6. Formation of the 14(13→12)-*abeo*-lathyrane epoxide **10** from the TBHP−$VO(acac)_2$ epoxidation of lathyrol (**7d**)

tronic nature (enone vs. allylic alcohol). The epoxidation of the enone system is seemingly related to the unique topology of the lathyrane system, which hinders co-planarity between the 14-oxo group and the adjacent double bond,[3] and places the 15-hydroxy group close to the endocyclic double bond, thus making it possible for metal ion complexation and delivery of the oxygen atom to the enone double bond.[18]

Conclusion

An efficient synthetic protocol for the epoxidation of lathyrol esters has been devised, affording candidates suitable for further transformation into other classes of *Euphorbia* diterpenoids. Since lathyrol esters are the only *Euphorbia* diterpenoids available in synthetically useful amounts from a commercial source,[7] their activation toward transannular cyclisation by epoxidation is a fundamental operation to devise synthetic mimics of the complex and still unexplored steps involved in the biogenesis of phorboids. Finally, the stereochemical course of the epoxidation of lathyrol esters led to a revision of the configuration at C-6 of the *Euphorbia* Factor L_1, overturning a thirty-year misconception on the structure of this compound, and relocating it on the mainstream of the biogenesis of *Euphorbia* diterpenoids.

Experimental Section

General: CC: Merck Silica gel. − IR: Shimadzu DR 8001 spectrophotometer. − Optical Rotations: Perkin−Elmer 241 polarimeter. − NMR: ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded at room temperature with a Bruker ARX500 spectrometer with an inverse multinuclear 5-mm probe-head equipped with a shielded gradient coil. The spectra were recorded in $CDCl_3$, or in mixtures of $CDCl_3$ and CD_3OD, and the solvent signals for $CHCl_3$/$CDCl_3$ (δ = 7.26 and 77.0, respectively) were used as reference. The chemical shifts (δ) are given in ppm, and the coupling constants (*J*) in Hz. COSY, HMQC, and HMBC experiments were recorded with gradient enhancements using sine-shaped gradient pulses. For the 2D heteronuclear correlation spectroscopy the refocusing delays were optimised for $^1J_{CH}$ = 145 Hz and $^nJ_{CH}$ = 10 Hz. The raw data were transformed and the spectra were evaluated with the standard Bruker UXNMR software (rev. 941001). − CH_2Cl_2 was dried by distillation from CaH_2, and Na_2SO_4 was used to dry solutions before the solvent evaporation. Methyltrioxorhenium and MCPBA were employed as obtained. Solutions of DMD[19] and TFD[20] in their parent ketones were prepared according to literature procedures and added to chilled (−15 °C) solutions of the olefin substrates in CH_2Cl_2. *Euphorbia* diterpenoids strongly retain solvents and are not generally amenable to elemental analysis. The purity of all compounds was checked by chromatographic methods (HPLC, TLC) and by careful analysis of the NMR spectra.

Epoxidation of the *Euphorbia* Factor L_3 (7a): To a suspension of the *Euphorbia* factor L_3 (**7a**) (300 mg, 0.57 mmol) in acetonitrile (8.0 mL), 10^{-4} M Na_2EDTA (6.0 mL) was added. After cooling to 0 °C, trifluoroacetone (0.51 mL, 643 mg, 5.7 mmol, 10 mol. equiv.) was added, followed by solid $NaHCO_3$ (4.30 g, mmol, 7 mol. equiv.) and oxone (4.02 g, mmol, 7 mol-equiv.). After stirring 1 h at 0 °C, further trifluoroacetone, $NaHCO_3$ and oxone were added (same amounts as the first addition), and stirring was continued for another hour, until TLC [petroleum ether/EtOAc (8:2); R_f(**7a**) = 0.38; R_f(**8a**) = 0.20] showed the complete disappearance of the starting material. The reaction mixture was worked up by dilution with water (ca. 20 mL) and extraction with $CHCl_3$ (2 × 50 mL). The pooled organic phases were washed with brine and dried (Na_2SO_4). Removal of the solvent gave 308 mg of crude **8a** as a white powder. Washing with ether afforded an analytical sample (279 mg, 88%), white powder, m.p. 195−198 °C. − $[\alpha]_D^{25}$ = −118 (CH_2Cl_2, *c* = 0.90) − IR (KBr): $\tilde{\nu}$ = 3856 cm^{-1} (OH), 1716 (C=O), 1655 (C=C), 1624 (C=C), 1273, 1232, 1209, 1107, 713. − ^1H NMR ($CDCl_3$): δ = 7.96 (d, *J* = 8.3 Hz, Bz), 7.54 (t, *J* = 7.5 Hz, Bz), 7.40 (t, *J* = 8 Hz, Bz), 6.62 (d, *J* = 11.4 Hz, 12-H), 6.30 (d, *J* = 8.9 Hz, 5-H), 5.68 (dd, *J* = 3 Hz, 3-H), 3.42 (dd, *J* = 14.1, 8.1 Hz, 1-H_α), 2.46 (d, *J* = 3.4 Hz, 17-H_a), 2.30 (m, 17-H_b), 2.21 (m, 2-H), 2.20 (s, 15-Ac), 2.05 (m, 7-H_β); 2.00 (m, 8-H_α), 1.94 (dd, *J* = 3.2, 8.9 Hz, 4-H), 1.84 (s, 20-H_3), 1.78 (s, 5-Ac), 1.73 (m, 8-H_β), 1.57 (dd, *J* = 14.1, 12.7 Hz, 1-H_β), 1.46 (dd, *J* = 8.2, 11.4 Hz, 11-H), 1.19 (s, 19-H_3), 1.17 (s, 18-H_3), 1.06 (m, 9-H), 0.88 (m, 7-H_α), 0.86 (d, *J* = 6.7 Hz, 16-H_3). − ^{13}C NMR ($CDCl_3$): δ = 196.6 (s, C-14), 170.2 (s, 5-Ac), 169.4 (s, 15-Ac), 165.7 (s, Bz), 143.6 (d, C-12), 136.0 (s, C-13) 133.1 (d, *p*-Bz), 129.8 (s, *i*-Bz), 129.6 (d, *o*-Bz), 128.7 (d, *m*-Bz), 92.0 (s, C-15), 80.8 (d, C-3), 65.0 (d, C-5), 58.9 (s, C-6), 55.2 (t, C-17), 49.9 (d, C-4), 48.0 (t, C-1), 38.1 (d, C-2), 34.8 (d, C-9), 33.4 (t, C-7), 29.1 (d, C-11), 28.9 (q, C-18), 25.6 (s, C-10), 21.8 (s, 15-Ac), 20.6 (s, 5-Ac), 20.0 (t, C-8), 16.7 (q, C-19), 14.0 (q, C-16), 12.4 (q, C-20). − HRMS (70 eV); *m*/*z*: 538.2573 (calcd. for $C_{31}H_{38}O_8$ 538.2567).

Epoxidation of the Deoxy *Euphorbia* Factor L_1 (7b): The same protocol employed for the epoxidation of the *Euphorbia* factor L_3 was used. The reaction course was followed by TLC [petroleum ether/EtOAc (8:2); R_f(**7b**) = 0.28; R_f(**8b**) = 0.16]. The crude reaction

product (516 mg from 500 mg of starting material) was washed with ether to afford 476 mg (92%) of analytical product, identical (^{1}H NMR, IR, m.p.) with the *Euphorbia* factor L_1.

Hydrolysis of the *Euphorbia* Factor L_1 (8b): A sample of the *Euphorbia* factor L_1 (2.0 g, 3.6 mmol) was suspended in 5% KOH in methanol (50 mL). After stirring for ca. 20 min at room temp., a clear solution was obtained, and stirring was continued until TLC [petroleum ether/EtOAc (2:8), R_f(**8b**) = 0.80] showed the complete disappearance of the starting material. After ca. 8 h, the reaction mixture was worked up by dilution with water (ca. 200 mL) and extraction with EtOAc (3 × 100 mL). The pooled organic phases were washed with brine, dried, and concentrated. The residue was purified by CC on silica gel [hexane/EtOAc (6:4)] to afford 114 mg (9%) of **8c** and 1.17 g (81%) of **9**. Epoxylathyrol (**8c**) was obtained as a white powder, m.p. 184−186 °C. − $[\alpha]_D^{25}$ = −76 (CH_2Cl_2, *c* = 0.60). − IR (KBr): $\tilde{\nu}$ = 3496 cm^{-1} (OH), 1690 (C=O), 1628 (C=C), 1458, 1265, 1152, 1072, 1009. − ^{1}H NMR ($CDCl_3$): δ = 6.64 (d, *J* = 11.1 Hz, 12-H), 4.39 (m, 5-H), 4.26 (dd, *J* = 3 Hz, 3-H), 2.99 (dd, *J* = 14.3, 9.6 Hz, 1-H_α), 2.66 (d, *J* = 3.8 Hz, 17-H_a), 2.59 (d, *J* = 3.8 Hz, 17-H_b), 2.22 (m, 7-H_β), 2.04 (m, 2-H), 1.93 (m, 8-H_α), 1.89 (s, 20-H_3), 1.80 (m, 4-H), 1.67 (dd, *J* = 14.3, 10.8 Hz, 1-H_β), 1.42 (dd, *J* = 8.5, 11.0 Hz, 11-H), 1.30 (m, 8-H_β), 1.20 (m, 7-H_α), 1.15 (s, 19-H_3), 1.15 (s, 18-H_3), 1.12 (d, *J* = 6.7 Hz, 16-H_3), 1.05 (m, 9-H). − ^{13}C NMR ($CDCl_3$): δ: = 202.9 (s, C-14), 144.3 (d, C-12), 136.4 (s, C-13), 88.4 (s, C-15), 78.9 (d, C-3), 66.7 (d, C-5), 60.7 (s, C-6), 54.4 (t, C-17), 53.5 (d, C-4), 48.3 (t, C-1), 37.7 (d, C-2), 34.7 (d, C-9), 32.4 (t, C-7), 28.8 (q, C-18), 27.5 (d, C-11), 25.1 (s, C-10), 19.9 (t, C-8), 15.8 (q, C-19), 13.9 (q, C-16), 13.1 (q, C-20). − HRMS (70 eV); *m*/*z*: 350.2082 (calcd. for $C_{20}H_{30}O_5$ 350.2093). − Compound **9** was obtained as a white powder, m.p. 210−213 °C. − $[\alpha]_D^{25}$ = −44 (CH_2Cl_2, *c* = 0.60). − IR (KBr): $\tilde{\nu}$ = 3476 cm^{-1} (OH), 3429 (OH), 1700 (C=O), 1458, 1086, 1074, 1045, 1028. − ^{1}H NMR ($CDCl_3$:CD_3OD 19:1): δ = 4.06 (dd, *J* = 3, 4 Hz, 3-H), 3.88 (dq, *J* = 4.9, 6.5 Hz, 13-H), 3.70 (d, *J* = 12.5 Hz, 17-H_a), 3.54 (d, *J* = 12.5 Hz, 17-H_b), 3.49 (dd, *J* = 11.0, 4.9 Hz, 12-H), 3.30 (m, 5-H), 3.28 (s, 12-OCH_3), 2.79 (dd, *J* = 4.2, 8.9 Hz, 4-H), 1.88 (m, 1-H_a), 1.86 (m, 7-H_a), 1.65 (m, 1-H_b), 1.62 (m, 2-H), 1.45 (m, 8-H_a), 1.12 (m, 7-H_b), 1.10 (d, *J* = 6.5 Hz, 20-H_3), 0.96 (d, *J* = 6.5 Hz, 16-H_3), 0.95 (s, 18-H_3), 0.94 (m, 8-H_b), 0.86 (s, 19-H_3), 0.75 (dd, *J* = 8.7, 11.0 Hz, 11-H), 0.19 (dd, *J* = 9 Hz, 9-H). − ^{13}C NMR ($CDCl_3$:CD_3OD 19 :1): δ = 211.8 (s,C-14), 87.8 (s, C-15), 77.8 (d, C-12), 77.0 (d, C-3), 64.7 (s, C-6), 62.6 (d, C-17), 57.1 (d, C-5), 55.8 (q, 12-OMe), 47.7 (d, C-4), 46.8 (t, C-1), 41.2 (d, C-13), 36.5 (d, C-2), 28.5 (q, C-18), 28.0 (t, C-7), 27.1 (d, C-9), 25.4 (d, C-11), 18.8 (t, C-8), 17.7 (s, C-10), 15.6 (q, C-19), 12.6 (q, C-16), 10.3 (q, C-20). −HRMS (70 eV); *m*/*z*: 382.2358 (calcd. for $C_{21}H_{36}O_7$ 382.2355).

Epoxidation of Lathyrol (7d): To a solution of lathyrol (200 mg, 0.60 mmol) in dry CH_2Cl_2 (10 mL), $VO(acac)_2$ (47 mg, 0.18 mmol, 0.3 mol. equiv.) and TBHP (3 M in CH_2Cl_2, 0.40 mL, 1.2 mmol, 2 mol. equiv.) was added. The reaction course was followed by TLC [petroleum ether/EtOAc (2:8); R_f(**7d**) = 0.55; R_f(**10**) = 0.58]. After 4 h, the reaction mixture was worked up by filtration through Celite and washing with brine. The semi-crystalline residue was purified by filtration through a short column of silica gel [5.0 g, elution with petroleum ether/EtOAc (7:3)] to give 196 mg (91%) **10** as colorless needles, m.p. 176−178 °C. − $[\alpha]_D^{25}$ = −71 (MeOH, *c* = 0.80). − IR (KBr): $\tilde{\nu}$ = 3457 cm^{-1} (OH), 3349 (OH), 1719 (C=O), 1696 (C=O), 1449, 1358, 1208, 1152, 1024. − ^{1}H NMR ($CDCl_3$:CD_3OD, 19 :1): δ = 4.45 (d, *J* = 6.2 Hz, 5-H), 4.37 (d, *J* = 11.8 Hz, 12-H), 4.17 (dd, *J* = 3.6, 3.0 Hz, 3-H), 2.91 (d, *J* = 4.7 Hz, 17-H_a), 2.55 (dd, *J* = 14.3, 10.0 Hz, 1-H_a), 2.40 (d, *J* = 4.7 Hz, 17-H_b), 2.15 (s, 20-H_3), 2.04 (dd, *J* = 3.0, 6.2 Hz, 4-H), 1.99 (m, 2-H), 1.66 (dddd, *J* = 15, 10, 8, 2 Hz, 8-H_a), 1.59 (dd, *J* = 14.3, 10.0 Hz, 1-H_b), 1.41 (ddd, *J* = 15, 10, 4 Hz, 7-H_a), 1.37 (ddd, J_7 = 15, 9.8 Hz, 7-H_b), 1.14 (dd, *J* = 11.8, 8.7 Hz, 11-H), 0.98 (s, 19-H_3), 0.98 (s, 18-H_3), 0.97 (d, *J* = 6.5 Hz, 16-H_3) 0.82 (m, 8-H_b), 0.43 (ddd, J_{8a-9} = 12, 8, 2 Hz, 9-H). − ^{13}C NMR ($CDCl_3$:CD_3OD 19 :1): δ =: 215.9 (s, C-14), 205.3 (s, C-13), 88.1 (s, C-15), 78.8 (d, C-3), 63.6 (d, C-5), 61.4 (s, C-6), 56.5 (d, C-4), 56.2 (d, C-12), 50.2 (t, C-17), 49.6 (t, C-1), 37.0 (d, C-2), 32.0 (t, C-7), 29.0 (q, C-20), 28.2 (q, C-18), 26.6 (d, C-11), 26.0 (t, C-9), 18.7 (s, C-10), 18.5 (t, C-8), 15.4 (q, C-19), 13.7 (q, C-16). − HRMS (70 eV); *m*/*z*: 366.2039 (calcd. for $C_{20}H_{30}O_6$ 366.2042).

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