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An improved synthesis of rhinocerotinoic acid

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Abstract—The stereoselective synthesis of *E*-rhinocerotinoic acid has been achieved in five steps from (−)-sclareol in an overall yield of 32%. This constitutes a significant improvement on the previous synthesis of this anti-inflammatory compound.

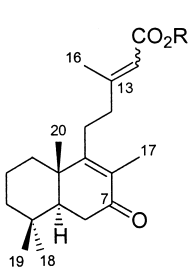
1. Introduction

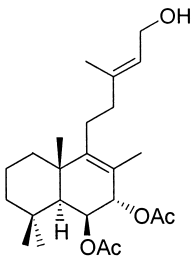
We required large quantities of rhinocerotinoic acid (**1**) as a starting material for a projected synthesis of 6β,7α-diacetoxylabda-8,13*E*-dien-15-ol (**2**) and its 6,7-diastereomers. Compound **2** is a bioactive metabolite isolated from the endemic South African intertidal marine mollusc, *Trimusculus costatus*[1] and we required more of this compound, and its 6,7-diastereomers, for comparative chemical ecology studies.

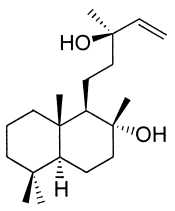
Rhinocerotinoic acid was originally obtained by Dekker et al.[2] from the South African medicinal plant *Elytropappus rhinocerotis* (commonly known as renosterbos) and was shown to have anti-inflammatory properties. Although this plant grows abundantly around Grahamstown, we found that local specimens of *E. rhinocerotis* did not contain any **1**. Consequently, we decided to synthesize **1** from commercially available (−)-sclareol (**3**) as briefly described by Dekker et al.[2] whereby **3** was first converted to methyl 13-hydroxy-7-oxolabda-8-en-15-oate (**4**) according to the route described by Mangoni and co-workers in the synthesis of grindelic acid (Scheme 1).[3] Dehydration of **4** with phosphorus oxychloride in pyridine followed by hydrolysis in alkaline medium resulted in the formation of rhinocerotinoic acid and isorhinocerotinoic acid (**5**). Unfortunately, this synthesis of **1** did not proceed smoothly in our hands and we report here an improved version.

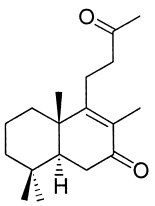
2. Results and discussion

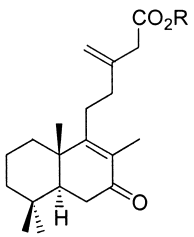
The degradative oxidation of **3** with potassium permanganate to yield (+)-8α-hydroxy-14,15-bisnorlabda-13-one (**6**)











1 Δ^{13} *E* R = H
5 Δ^{13} *Z* R = H
13 Δ^{13} *E* R = Et
14 Δ^{13} *Z* R = Et
17 Δ^{13} *E* R = Me
18 Δ^{13} *Z* R = Me

2

3

15

16 R = H
19 R = Me

Keywords: labdane; diterpene; rhinocerotinoic acid; synthesis.

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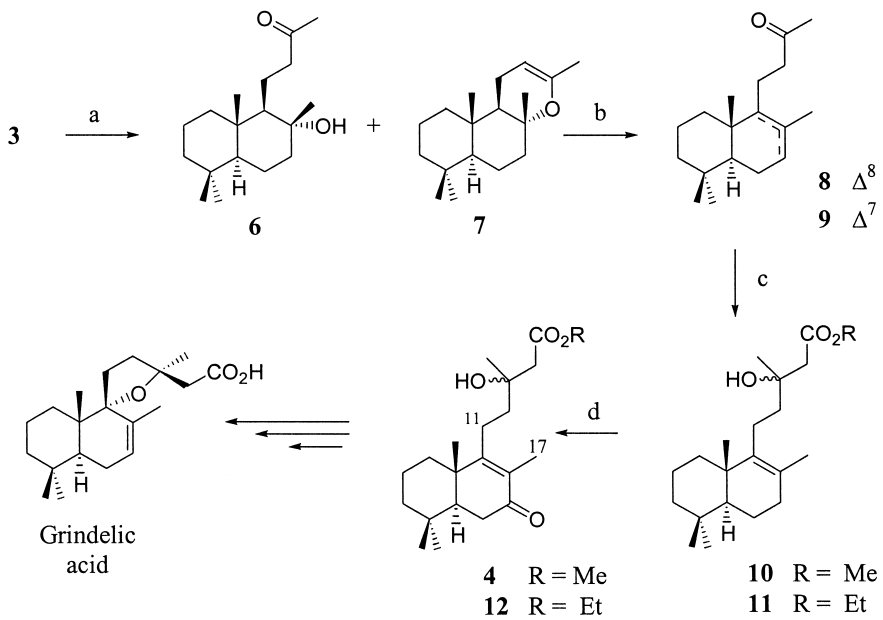

Scheme 1. Mangoni et al.'s synthesis of grindelic acid via **4**.[3] *Reagents and conditions*: (a) $KMnO_4$, acetone, <15°C; (b) I_2, benzene, △, 3 h; (c) Zn, $BrCH_2CO_2Me$, benzene–Et_2O (5:2), △, 2 h; (d) CrO_3, H_2SO_4, acetone, over-night, rt.

and the enol ether (+)-8α,13-epoxy-14,15-bisnorlabda-12-ene (**7**) was first reported by Ruzicka et al.[4] Barltrop and co-workers subsequently modified this procedure so that, under controlled conditions, either **6** or the enol ether **7** may be obtained as the major product of oxidation.[5,6] The facile conversion of **6** to **7** is well documented with significant cyclization and dehydration occurring in light petroleum,[5] benzene[7] or pyridine[8] solutions and quantitative conversion occurring in the presence of trace acid,[5] on silica gel[9] or through vacuum distillation.[10]

Although both **6** and **7** may be converted to (+)-14,15-bisnorlabda-8-en-13-one (**8**) by treatment with mineral acid in ethanol,[5] this procedure has subsequently been found to produce a mixture of the Δ^7- and Δ^8-unsaturated ketones.[11] As the second step in our synthesis involved the iodine catalyzed dehydration of **6**, we were careful to optimize the yield of this intermediate and avoid the formation of **7**. Accordingly, **3** was oxidized with potassium permanganate following the established procedure[5] to yield a 10:1 mixture (by ^1H NMR in benzene-d_6) of the desired product **6** and the enol ether **7** in 77% yield. Compounds **6** and **7** were obtained pure by recrystallization from hexane and methanol, respectively. Dehydration of **6** to **8** using iodine in refluxing benzene gave variable yields of **7**–**9**, and the yield of the desired product **8** was optimized as follows. Instead of using a small crystal of iodine,[12] we standardized the iodine concentration by adding a known volume of a solution of iodine in anhydrous benzene. The reaction was consequently carried out using 0.05 equiv. of iodine and monitored by NMR spectroscopic analysis of aliquots taken after 0, 0.5, 1, 2, 4, 6, 18 h reflux. This showed that **6** rapidly formed the enol ether **7**, which on further reaction rearranged, initially to the kinetically favored Δ^7-unsaturated ketone **9**, then to the more thermodynamically favored **8**. Optimal conditions for the dehydration were 6 h reflux with 0.05 equiv. of iodine, which gave **8** and **9** in 75 and 6% yield, respectively, as colorless oils, easily separable by flash chromatography. The proposed intermediacy of **7** was confirmed by subjecting it to the same dehydration conditions. Similar yields of **8** (76%) and **9** (8%) were obtained, indicating that in subsequent large-scale (5–7 g) preparations of **8** the products obtained from the initial permanganate oxidation step need not be separated before continuing with the dehydration.

The iodine catalyzed dehydration procedure gave a better yield of **8** than acid catalyzed dehydration.[5] In accordance with the observations of Wenkert et al.[11] we found that when dehydrated under acidic conditions, **6** gave a 71% overall yield of **8** and **9** in a 3:2 ratio, and **7** gave a 67% overall yield of **8** and **9** in a 2:1 ratio. Moreover, the products of acid catalyzed dehydration were identical to those obtained through iodine catalyzed dehydration, contrary to the results reported by Mangoni and Belardini.[12] With a reliable, gram scale preparation of the key intermediate **8** in hand, we next turned our attention to the formation of methyl 13-hydroxylabda-8-en-15-oate (**10**) by Reformatsky reaction[13] but, owing to the commercial availability of ethyl bromoacetate, we instead prepared the ethyl ester **11** in 93% yield as a 1:1 mixture (determined by ^1H and ^{13}C NMR spectroscopy) of inseparable C-13 epimers. Although the allylic oxidation of the methyl ester **10** to **4** using Jones' reagent (Scheme 1) was reported to proceed in 86% yield,[3] we obtained a complex mixture of products in low yield with the ethyl ester **11**, presumably because of competing allylic oxidation at C-11 and C-17. However, when we applied the Chu and Coates modification[14] of the Collins oxidation[15] using 15 equiv. of dipyridine–chromium trioxide, the desired α,β-unsaturated ketone (**12**) was obtained in 80% yield.

The next transformation in the synthesis, dehydration of **12** with phosphorus oxychloride in pyridine,[16] proceeded regiospecifically to give a reasonable yield (76%) of dehydration products, although the stereoselectivity of this reaction was disappointing: the Δ^{13}-*E*-isomer, ethyl rhinocerotinoate (**13**), and the Δ^{13}-*Z*-isomer, ethyl

Table 1. ^{1}H (400 MHz, $CDCl_3$), ^{13}C (100 MHz, $CDCl_3$) and 2D NMR data of methyl 7-oxolabda-8,13(16)-dien-15-oate (**19**)

Carbon	δ_C ppm, (mult.)	δ_H ppm (int., mult., *J*, Hz)	HMBC correlation to	COSY coupling to
1	35.7 (t)	1.34 (1H, bt, 11.1), 1.90 (1H, bd, 12.4)	C-2, C-10	H_2-2
2	18.6 (t)	1.58 (2H, m)	C-1, C-2	H_2-1, H_2-3
3	41.3 (t)	1.21 (1H, bt, 13.3), 1.46 (1H, bd, 13.1)	C-2, C-19	H_2-2
4	33.1 (s)			
5	50.2 (d)	1.68 (1H, bd, 13.8)	C-4, C-6, C-7, C-10	H_2-6
6	35.2 (t)	2.34 (1H, bt, 13.9), 2.47 (1H, bd, 17.2)	C-5, C-7, C-8, C-9, C-10	H-5
7	200.1 (s)			
8	130.3 (s)			
9	167.2 (s)			
10	40.9 (s)			
11	27.8 (t)	2.31 (2H, m)	C-9, C-10, C-12, C-13,	H_2-12
12	34.6 (t)	2.22 (2H, bd, 7.5)	C-13, C-16	H_2-11, H_2-16
13	141.8 (s)			
14	41.8 (t)	3.08 (2H, bs)	C-12, C-13, C-15, C-16	H_2-16
15	171.6 (s)			
16	114.0 (t)	4.95 (1H, s), 4.98 (1H, s)	C-12, C-13, C-14, C-15	H_2-12, H_2-14
17	11.3 (q)	1.74 (3H, s)	C-7, C-8, C-9	
18	32.5 (q)	0.87 (3H, s)	C-4, C-5, C-10, C-19	
19	21.3 (q)	0.90 (3H, s)	C-3, C-4, C-5, C-18	
20	18.1 (q)	1.07 (3H, s)	C-1, C-5, C-9, C-10	
15-OMe	51.9 (q)	3.68 (3H, s)	C-15	

isorhinocerotinoate (**14**), were obtained in a 2:1 ratio and were only separable by normal phase semi-preparative HPLC. Repetition of this procedure using the more active dehydrating agent thionyl chloride[17] gave a complex mixture of products in low yield, which was not investigated further. The unsatisfactory stereoselectivity observed above prompted us to try boron trifluoride etherate, which has been reported to yield the thermodynamically favored elimination products in higher yields than classical reagents,[18] but only starting material was recovered on leaving a solution of this reagent and **12** in dichloromethane at room temperature for 24 h. Unfortunately, neither refluxing with catalytic amounts of iodine in benzene[19] nor prolonged heating with thiophenol[20] satisfactorily converted **14** in the 2:1 mixture to **13**.

Accordingly, the synthesis was modified by using the Horner–Wadsworth–Emmons (HWE) modification of the Wittig reaction, which has been widely used in the stereoselective preparation of both *E* and *Z* disubstituted α,β unsaturated esters,[21,22] even though the stereoselectivity is often significantly diminished when using ketones to prepare trisubstituted alkenes.[23] To use this methodology, we had to perform the allylic oxidation at C-7 prior to elaboration of the side chain and rely on the HWE olefination to proceed selectively at the more electrophilic saturated C-13 carbonyl group in the known diketone **15**.[24] Such preferential reaction is well known, e.g. with the Wieland–Miescher ketone.[25–27] Accordingly, **8** was submitted to Collins' oxidation,[14] employing the optimized procedure already described, to afford (+)-14,15-bisnorlabda-8-en-7,13-dione (**15**)[24] in 81% yield. Compound **15** was then subjected to HWE reaction with triethyl phosphonoacetate in tetrahydrofuran to give the α,β-unsaturated esters **13** and **14** with vastly improved stereoselectivity (10:1 *E*/*Z*) and in excellent yield (96%). Although the chemospecificity observed in the HWE reaction was predictable, the extent of stereoselectivity was unexpected[23] as HWE reactions performed on similar 14,15-bisnorlabda-13-one derivatives under comparable conditions generally exhibit less stereoselectivity than that obtained with **15**.[28–30]

Having established a method of preparing the C-13–C-14 double bond stereoselectively, we turned our attention to the hydrolysis of the ester functionality in **13** which, according to Dekker et al.[2] had been carried out under basic conditions. However, ^{1}H NMR examination of the crude reaction mixture obtained by refluxing the 10:1 mixture of esters **13** and **14** with ethanolic potassium hydroxide suggested that significant isomerization of the C-13–C-14 double bond had occurred. The presence of two vinylic methine singlets at δ_H 5.73 and 5.72 indicated that both **1** and **5** were present and additional vinylic methylene singlets at δ_H 5.00 and 5.02 suggested that 7-oxolabda-8,13(16)-dien-15-oic acid (**16**) had also been formed. Integration of the vinylic proton resonances showed that the crude reaction mixture contained these acids in a ratio of 12:3:2, respectively. Attempts to separate this mixture by chromatographic methods (normal phase and reversed phase column chromatography and HPLC) were unsuccessful. Crystallization from hexane allowed the isolation of approximately half of the *E*-isomer **1** while crystallization of the mother liquors from methanol–water yielded a small quantity of the pure *Z*-isomer **5**. The mother liquors from **5** were methylated with diazomethane and the resulting methyl esters separated by repeated flash chromatography (the ethyl esters were inseparable under these conditions), followed by semi-preparative HPLC to give methyl rhinocerotinoate (**17**), methyl isorhinocerotinoate (**18**) and methyl 7-oxolabda-8,13(16)-dien-15-oate (**19**). The structure of the new ester **19** was elucidated from a combination of NMR spectroscopic data (Table 1) and high resolution mass spectrometry.

As Dekker et al.[2] did not report any isomerization resulting from hydrolysis of the mixed methyl esters **17** and **18**, nor stipulate the base used for hydrolysis, the ethyl esters **13** and **14** were also saponified with a weaker base (potassium carbonate) but the same products, **1**, **5**, and **16**, were

obtained in 83% yield and a less favorable ratio of 7:2:7, respectively. A milder method for cleaving esters was also attempted and the mixture of the ethyl esters **13** and **14** was refluxed with chlorotrimethylsilane and sodium iodide in acetonitrile.[31] Unfortunately, only a complex mixture of products (from ^{1}H NMR) resulted. A search of the literature for the saponification of related β-methyl β-alkyl substituted α,β-unsaturated esters indicated that isomerization of the double bond is extremely variable.[32] In such systems this transformation has been reported to proceed with no isomerization,[33] with *cis–trans* isomerization,[34] as well as minor α,β- to βγ-isomerization[35] of the double bond. We also attempted to hydrolyze the 10:1 mixture of **17** and **18** under acidic conditions using the method of Cativela et al.[36] by heating the esters with HCl in THF at 70°C. No isomerization occurred but poor yields of the acids resulted, necessitating an investigation of other solvents and mineral acids to facilitate hydrolysis. The best yield (82%) was obtained on heating **13** and **14** (4 h) with H_2SO_4 in acetic acid. Washing the product with hexane followed by vacuum sublimation afforded isomerically pure (by ^{1}H NMR) rhinocerotinoic acid (**1**) in 72% overall yield. Methyl 7-oxolabda-8,13(16)-dien-15-oate (**19**) on similar acid hydrolysis isomerized to give a 3:2 mixture (by ^{1}H NMR) of **1** and **5**.

In conclusion, the overall yield of our five step synthesis of **1** from (−)-sclareol was 32%. Dekker et al.[2] do not quote yields in their six step synthesis but previous results for the preparation of **4**[3,12] and our own for the subsequent dehydration and saponification suggest an overall yield for their synthesis of not more than 12%.

3. Experimental

3.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz Avance NMR spectrometer using $CDCl_3$ as the solvent, referenced at δ 7.25 and 77.0, respectively. The HRFABMS data were acquired by Professor Louis Fourie of the University of Potchefstroom on a Micromass 70-70E spectrometer and the LREI mass spectra (70 eV) were obtained on a Finnegan-Matt GCQ mass spectrometer by Mr Aubrey Sonemann of Rhodes University. The IR data for all compounds were obtained from thin films on NaCl discs using a Perkin–Elmer 2000 FTIR spectrometer. All rotations were recorded on a Perkin–Elmer 141 polarimeter as $CHCl_3$ solutions. Melting points were determined using a Reichert hot-stage microscope and are uncorrected. Reactions with exclusion of moisture were performed in flame-dried glassware under N_2. Immediately prior to their use in dry reactions, diethyl ether, tetrahydrofuran and benzene were distilled from sodium metal/benzophenone ketyl, and dichloromethane was distilled from calcium hydride. Pyridine was distilled at reduced pressure from KOH and stored over 4 Å molecular sieves under nitrogen. General laboratory solvents were distilled before use. Reactions were monitored by analytical normal phase (performed on DC-Plastikfolien Kieselgel 60 F_{254} plates) or reverse phase (performed on DC-Ferigplatten RP18 F_{254} plates) thin layer chromatography visualized under UV light (254 nm) and developed by spraying with 10% H_2SO_4 in MeOH followed by heating. Open column chromatography was performed using Kieselgel 60 (70–230 mesh) silica gel and flash chromatography was performed using Kieselgel 60 (230–400 mesh) silica gel. Normal phase semi-preparative HPLC separations were performed on a Whatman Magnum 9 Partisil 10 column with an eluent flow rate of 4 mL min^{-1} and reverse phase semi-preparative HPLC separations were attempted on a Phenomenex Luna 10 μm C18 column.

3.2. Attempted isolation of rhinocerotinoic acid from *E. rhinocerotis*

Dried aerial parts (312 g) of *E. rhinocerotis* (identified by Mrs Estelle Brink of the Albany Museum Herbarium, Grahamstown), collected from Burnt Kraal near Grahamstown in early November 1999 were extracted in a Soxhlet apparatus with acetone. The extract was concentrated in vacuo and the resulting green waxy solid (11.8 g) stirred with Et_2O (500 mL), left overnight at 5°C and filtered. Portions of the green filtrate (10 mL) were extracted with either 5% $NaHCO_3$ or Na_2CO_3 solutions (10 mL), the aqueous phase acidified, extracted with Et_2O, dried and evaporated. Both acidic extracts were examined by ^{1}H NMR spectroscopy, but no resonances corresponding to those reported for rhinocerotinoic acid were observed. In case **1** was present as an ester in the *E. rhinocerotis* extract, the neutral material from the base extractions was refluxed with 8% ethanolic KOH for 18 h but no **1** could be detected in the product by ^{1}H NMR spectroscopy.

3.3. Potassium permanganate oxidation of (−)-sclareol (3)

Sclareol (25.0 g, 81.2 mmol) was dissolved in a mixture of acetone (2.5 L) and water (25 mL) in a flask previously washed with aqueous Na_2CO_3, cooled (15°C) and finely powdered $KMnO_4$ (45.0 g, 285 mmol, 3.5 equiv.) added in portions over 2 h. The reaction mixture was stirred for a further 5 h and left at ambient temperature overnight. The solution was carefully siphoned from the fine MnO_2 precipitate which was washed with acetone (2×600 mL). The combined acetone extracts were concentrated to 300 mL under reduced pressure, filtered through celite, 10% aqueous NaOH (50 mL) added, and the remaining acetone removed in vacuo. The residual semi-solid solution was extracted with EtOAc (1×200 mL, 1×100 mL) which was washed with H_2O (3×15 mL), dried and concentrated to afford crude 8α-hydroxy-14,15-bisnorlabda-13-one (**6**, 17.4 g, mp 71–75°C). Washing with hexane afforded **6** (15.9 g, 56.8 mmol, 70%) and the mother liquors, on evaporation, gave **7** (1.43 g, 5.46 mmol, 7%).

3.3.1. (+)-8α-Hydroxy-14,15-bisnorlabda-13-one (6). White solid (from hexane); mp 81–82°C, lit.[6] 78–80°C; $[\alpha]_D^{27}$=+5 (*c* 1.08), lit.[7] +6.7; IR, ^{1}H and ^{13}C NMR data consistent with published values;[7] EIMS *m/z* (rel. int.) 280 [M$^+$] (2), 262 (77), 244 (41), 191 (56), 229 (95), 191 (56), 177 (46), 121 (63), 109 (100), 95 (91); HRFABMS obsd 280.2405 [M$^+$], $C_{18}H_{32}O_2$ requires 280.2402.

3.3.2. (+)-8α,13-Epoxy-14,15-bisnorlabda-12-ene (7). Fine white solid (from ice-cold MeOH); mp 43–45°C,

lit.[5] 44–46°C; $[\alpha]_D^{26}$=+4 (*c* 3.53), lit.[5] +5; IR, ^{1}H and ^{13}C NMR data consistent with published values;[7] EIMS *m/z* (rel. int.) 262 [M^+] (95), 244 (45), 229 (98), 191 (67), 135 (54), 121 (67), 109 (98), 95 (100), 81 (97); HRFABMS obsd [M^+] 262.2294, $C_{18}H_{30}O$ requires 262.2297.

3.4. Conversion of (+)-8α-hydroxy-14,15-bisnorlabda-13-one (6) to (+)-8α,13-epoxy-14,15-bisnorlabda-12-ene(7)

The hydroxy ketone **6** (2.04 g, 7.29 mmol) was slowly passed through an open column of silica gel (100 g) using $CHCl_3$ as eluent. Removal of the solvent in vacuo gave a quantitative yield of the enol ether **7**.

3.5. Iodine catalysed dehydration of (+)-8α-hydroxy-14,15-bisnorlabda-13-one (6) and isomerization of (+)-8α,13-epoxy-14,15-bisnorlabda-12-ene (7)

The hydroxy ketone **6** (5.00 g, 17.9 mmol) was dissolved in anhydrous benzene (500 mL), I_2 (0.23 g, 0.9 mmol, 0.05 equiv.) added and the resulting pink solution refluxed under a Dean-Stark head for 6 h. The solution was washed with 5% $Na_2S_2O_3$ (3×25 mL) and H_2O (25 mL), dried ($MgSO_4$) and concentrated to give a dark brown oil (4.39 g) that was purified by flash chromatography on silica gel in 9:1 hexane/EtOAc to give (+)-14,15-bisnorlabda-7-ene-13-one (**9**, 0.26 g, 0.99 mmol, 6%) and (+)-14,15-bisnorlabda-8-ene-13-one (**8**, 3.51 g, 13.4 mmol, 75%) as light yellow oils.

The enol ether **7** (5.20 g, 19.7 mmol) was treated in the same manner to give a dark brown oil (5.18 g), which after flash chromatography yielded the unsaturated ketones **9** (0.41 g, 1.56 mmol, 8%) and **8** (3.91 g, 14.9 mmol, 76%) as light yellow oils.

3.5.1. (+)-14,15-Bisnorlabda-7-ene-13-one (9). Oil; $[\alpha]_D^{27}$=+22 (*c* 1.60), lit. for enantiomer[28] −23.1; IR ν_{max} 2924, 2847, 1717, 1669, 1457, 1388, 1360, 1214, 1160, 983 cm^{-1}; ^{1}H NMR δ 5.40 (1H, br s, H-7), 2.62 (1H, m, H-12a), 2.40 (1H, m, H-12b), 2.12 (3H, s, H_3-16), 1.93 (1H, m, H-6a), 1.88 (1H, m, H-6b), 1.85 (1H, m, H-1a), 1.79 (1H, m, H-11a), 1.64 (3H, s, H_3-17), 1.58 (1H, s, H-9), 1.52 (1H, m, H-2a), 1.44 (1H, m, H-2b), 1.41 (1H, m, H-11b), 1.40 (2H, m, H_2-3), 1.15 (1H, dd, *J*=12.3, 4.9 Hz, H-5), 0.93 (1H, dd, *J*=13.7, 4.3 Hz, H-1b), 0.86 (3H, s, H_3-19), 0.84 (3H, s, H_3-18), 0.76 (3H, s, H_3-20); ^{13}C NMR δ 208.8 (s, C-13), 134.5 (s, C-8), 123.0 (d, C-7), 54.4 (d, C-9), 50.5 (d, C-5), 45.9 (t, C-12), 42.3 (t, C-3), 39.4 (t, C-1), 36.9 (s, C-10), 33.2 (q, C-18), 33.0 (s, C-4), 29.9 (q, C-16), 23.8 (t, C-6), 22.2 (q, C-17), 21.9 (q, C-19), 21.0 (t, C-11), 18.8 (t, C-2), 13.6 (q, C-20); EIMS *m/z* (rel. int.) 262 [M^+] (5), 244 (25), 229 (19), 204 (83), 189 (55), 161 (100), 147 (24), 119 (35), 105 (41); HRFABMS obsd 262.2296 [M^+], $C_{18}H_{30}O$ requires 262.2297.

3.5.2. (+)-14,15-Bisnorlabda-8-ene-13-one (8). Oil; $[\alpha]_D^{26}$=+75 (*c* 1.10), lit.[12] +78; IR ν_{max} 2938, 2867, 1716, 1463, 1387, 1360, 1273, 1159, 1070, 999 cm^{-1}; ^{1}H NMR δ 2.47 (2H, t, *J*=8.3 Hz, H_2-12), 2.28 (1H, m, H-11a), 2.16 (1H, m, H-11b), 2.12 (3H, s, H_3-16), 1.97 (2H, m, H_2-7), 1.77 (1H, br d, *J*=12.2 Hz, H-1a), 1.64 (1H, m, H-6a), 1.57 (1H, m, H-2a), 1.52 (3H, s, H_3-17), 1.47 (1H, m, H-2b), 1.42 (1H, m, H-3a), 1.36 (1H, m, H-6b), 1.12 (1H, m, H-3b), 1.08 (1H, dd, *J*=12.5, 1.9 Hz, H-5), 1.07 (1H, m, H-1b), 0.93 (3H, s, H_3-20), 0.87 (3H, s, H_3-18), 0.82 (3H, s, H_3-19); ^{13}C NMR δ 208.9 (s, C-13), 139.5 (s, C-9), 126.6 (s, C-8), 52.0 (d, C-5), 44.7 (t, C-12), 41.8 (t, C-3), 39.1 (s, C-10), 37.0 (t, C-1), 33.7 (t, C-7), 33.3 (s, C-4), 33.3 (q, C-18), 29.7 (q, C-16), 21.7 (q, C-19), 21.6 (t, C-11), 20.0 (q, C-20), 19.4 (q, C-17), 19.0 (t, C-6 and t, C-2); EIMS *m/z* (rel. int.) 262 [M^+] (9), 244 (58), 229 (100), 204 (32), 189 (73), 173 (71), 159 (63), 133 (67), 105 (67), 91 (60); HRFABMS obsd 262.2295 [M^+], $C_{18}H_{30}O$ requires 262.2297.

3.6. Acid catalyzed dehydration of (+)-8α-hydroxy-14,15-bisnorlabda-13-one (6) and isomerization of (+)-8α,13-epoxy-14,15-bisnorlabda-12-ene (7)

The hydroxy ketone **6** (1.43 g, 5.11 mmol) was dissolved in EtOH (50 mL), 5 M HCl (10 mL) added and the solution heated at 70°C for 2 h. The reaction mixture was concentrated in vacuo to 20 mL, poured into H_2O (100 mL) and extracted with EtOAc (3×50 mL). The organic fractions were combined, washed with 5% Na_2CO_3 (50 mL), dried (Na_2SO_4) and concentrated to give a yellow oil (1.21 g). Silica gel flash chromatography of the crude product in 9:1 hexane/EtOAc afforded the unsaturated ketones **9** (0.36 g, 1.37 mmol, 27%) and **8** (0.59 g, 2.25 mmol, 44%) as light yellow oils.

The enol ether **7** (1.29 g, 4.92 mmol) was treated in the same manner to give a light yellow oil (1.08 g) that yielded, after flash chromatography, the unsaturated ketones **9** (0.30 g 1.15 mmol, 23%) and **8** (0.56 g, 2.18 mmol, 44%) as light yellow oils.

3.7. Preparation of ethyl 13-hydroxylabda-8-en-15-oate (11) via the Reformatsky reaction

Activated zinc powder (2.10 g, 32.2 mmol, 1.2 equiv.; washed with 10% HCl for 5 min, rinsed twice with water, twice with acetone and dried in an oven at 120°C for 1 h immediately prior to use) and ethyl bromoacetate (3.59 mL, 32.2 mmol, 1.2 equiv.) were stirred in a mixture of anhydrous benzene (30 mL) and anhydrous Et_2O (10 mL). The mixture was gently warmed at 40°C until reaction between the zinc and ethyl bromoacetate caused the solvent to reflux. When this reaction was complete, **8** (7.04 g, 26.9 mmol) in a mixture of anhydrous benzene (30 mL) and anhydrous Et_2O (10 mL) was added dropwise over 10 min and the resulting solution gently refluxed for 2.5 h. The solution was cooled, poured into 2 M H_2SO_4 (30 mL) and extracted with Et_2O (3×20 mL). The organic fractions were combined, washed with 5 % $NaHCO_3$ (2×20 mL) and H_2O (10 mL), dried ($MgSO_4$) and concentrated to give a yellow oil (10.3 g). Silica gel flash chromatography in 7:3 hexane/EtOAc afforded ethyl 13-hydroxylabda-8-en-15-oate (**11**, 8.74 g, 25.0 mmol, 93%) as a 1:1 mixture of C-13 diastereomers (determined from ^{1}H and ^{13}C NMR spectroscopy; inseparable by normal phase HPLC) and recovered starting material (**8**, 331 mg, 1.26 mmol, 5%).

3.7.1. Ethyl 13-hydroxylabda-8-en-15-oate (11). Oil; IR ν_{max} 3523 (br), 2939, 2926, 1716, 1463, 1374, 1332, 1103,

1030 cm^{-1}; ^1H NMR δ 4.16 (2H,q, J=7.1 Hz, 15-OCH_2CH$_3$), 3.53/3.52 (1H, s, 13-OH), 2.52 (1H, d, J=15.6 Hz, H-14a), 2.48 (1H, d, J=15.6 Hz, H-14b), 2.08 (1H, m, H-11a), 1.98 (1H, m, H-11b), 1.88 (1H, m, H-7b), 1.78 (1H, J=14.0 Hz, H-1a), 1.67 (1H, m, H-2a), 1.56 (2H, m, H_2-12), 1.54/1.53 (3H, s, H_3-17), 1.43 (1H, m, H-2b), 1.38 (2H, m, H_2-6), 1.26 (3H, t, J=7.1 Hz, 15-OCH$_2$CH_3), 1.24 (3H, s, H_3-16), 1.14 (2H, m, H_2-3), 1.11 (1H, m, H-1b), 1.07 (1H, m, H-5), 0.93 (3H, s, H_3-18), 0.86 (3H, s, H_3-20), 0.81 (3H, s, H_3-19); ^{13}C NMR δ 173.1 (s, C-15), 139.8 (s, C-9), 125.9 (s, C-8), 71.2 (s, C-13), 60.6 (t, 15-OCH$_2$CH$_3$), 51.9 (d, C-5), 44.6 (t, C-14), 42.1 (t, C-3), 42.0 (t, C-12), 41.8 (t, C-6), 39.1 (s, C-10), 37.0 (t, C-1), 33.6 (t, C-7), 33.3 (q, C-20 and s, C-4), 26.4 (q, C-16), 22.1 (t, C-11), 21.7 (q, C-19), 20.1 (q, C-18), 19.4 (q, C-17), 19.1 (t, C-2), 14.1 (q, 15-OCH$_2$CH$_3$); EIMS m/z (rel. int.) 350 [M^+] (3), 332 (12), 317 (13), 271 (31), 229 (54), 204 (100), 189 (57), 161 (46), 121 (41), 95 (27); HRFABMS obsd 350.2821 [M^+], $C_{22}H_{38}O_3$ requires 350.2821.

3.8. Allylic oxidation of ethyl 13-hydroxylabda-8-en-15-oate (11)

CrO_3 (18.9 g, 189 mmol, 15 equiv.; dried at 0.5 mm Hg and 70°C over P_2O_5 for 8 h immediately prior to use) was stirred vigorously in anhydrous CH_2Cl_2 (200 mL) and cooled in an ice-salt bath. Pyridine (30.5 mL, 379 mmol, 30 equiv.) in CH_2Cl_2 (50 mL) was then added dropwise over 30 min taking care not to allow the temperature to rise above 0°C. The resulting deep red solution was allowed to warm to ambient temperature over 1 h and stirred for a further 30 min before ethyl 13-hydroxylabda-8-en-15-oate (**11**, 4.42 g, 12.6 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 30 min. The solution was stirred at room temperature for 48 h, during which time a large amount of waxy, dark brown precipitate formed. The supernatant solution was decanted, the precipitate thoroughly washed with EtOAc (3×100 mL) and the washings combined with the supernatant solution. The tarry precipitate was dissolved in sat. $NaHCO_3$ (500 mL) and this solution extracted with EtOAc (2×100 mL; centrifugation helped to break the emulsions which formed). The organic fractions were combined with the initial supernatant, the volume of the resulting solution reduced to approximately 200 mL in vacuo and then thoroughly washed with 1.5 M NaOH (3×100 mL), 1 M HCl (2×100 mL), 5% $NaHCO_3$ (1×100 mL) and sat. brine (1×50 mL). Drying ($MgSO_4$) and evaporation of the solvent gave a yellow oil (4.17 g) that, after flash chromatography in 3:2 hexane/EtOAc, afforded ethyl 13-hydroxy-7-oxolabda-8-en-15-oate (**12**, 1:1 mixture of C-13 diastereomers) as a light yellow oil (3.69 g, 10.1 mmol, 80%).

3.8.1. Ethyl 13-hydroxy-7-oxolabda-8-en-15-oate (12). Oil; IR ν_{max} 3437 (br), 2931, 2863, 1732, 1661, 1600, 1376, 1331, 1154, 1031 cm^{-1}; ^1H NMR δ 4.17 (2H, q, J=7.1 Hz, 15-OCH_2CH$_3$), 3.64/3.62 (1H, s, 13-OH), 2.53 (1H, d, J=15.9 Hz, H-14a), 2.47 (1H, d, J=17.5 Hz, H-6a), 2.43 (1H, d, J=15.9 Hz, H-14b), 2.33 (1H, m, H-6b), 2.30 (2H, m H_2-11), 1.19 (1H, br t, J=11.8 Hz, H-1a), 1.74/1.73 (3H, s, H_3-17), 1.68 (1H, m, H-2a), 1.66 (1H, m, H-5), 1.62 (2H, m, H_2-12), 1.55 (1H, m, H-2b), 1.46 (1H, br d, J=13.3 Hz, H-3a), 1.32 (1H, m, H-1b), 1.27 (3H, t, J=7.2 Hz, 15-OCH$_2$CH_3), 1.27 (3H, s, H_3-16), 1.20 (1H, dd, J=13.3, 4.1 Hz, H-3b), 1.07 (3H, s, H_3-18), 0.87 (3H, s, H_3-19), 0.86 (3H, s, H_3-20); ^{13}C NMR δ 200.1 (s, C-7), 172.9 (s, C-15), 167.7/167.6 (s, C-9), 130.2 (s, C-8), 70.9 (s, C-13), 60.8 (t, 15-OCH$_2$CH$_3$), 50.3 (d, C-5), 44.7 (t, C-14), 41.3 (t, C-3), 41.1 (s, C-10), 40.2/40.1 (t, C-12), 35.9 (t, C-1), 35.2 (t, C-6), 33.1 (s, C-4), 32.5 (q, C-20), 26.5/26.3 (q, C-16), 23.7 (t, C-11), 21.3 (q, C-19), 18.6 (t, C-2), 18.2 (q, C-18), 14.1 (q, 15-OCH$_2$CH$_3$), 11.2 (t, C-17); EIMS m/z (rel. int.) 364 [M^+] (1), 346 (38), 331 (16), 285 (16), 259 (19), 240 (63), 205 (48), 161 (22), 152 (83), 135 (100); HRFABMS obsd 365.2691 [(M+H)$^+$], $C_{22}H_{37}O_4$ requires 365.2692.

3.9. Dehydration of ethyl 13-hydroxy-7-oxolabda-8-en-15-oate (12)

Ethyl 13-hydroxy-7-oxo-labda-8-en-15-oate (**12**, 6.34 g, 17.4 mmol) was dissolved in anhydrous pyridine (40 mL), cooled to −10°C and $POCl_3$ (12.7 mL, 139 mmol, 8 equiv.) in dry pyridine (20 mL) added dropwise. The solution was slowly warmed to RT and allowed to stir for 16 h before the reaction was quenched by pouring into ice (300 g) and the resulting aqueous suspension extracted with EtOAc (3×100 mL). The organic phases were combined, washed with 1 M HCl (3×100 mL), 5% Na_2CO_3 (100 mL) and sat. brine (1×50 mL), dried (Na_2SO_4) and the solvent evaporated to give a brown oil (5.43 g). Silica gel flash chromatography of the crude product (7:3 hexane/EtOAc) yielded a 2:1 mixture (measured from integration of the H-14 vinylic proton resonances in the ^1H NMR spectrum of the purified product) of ethyl rhinocerotinoate (**13**) and ethyl isorhinocerotinoate (**14**) as a yellow oil (4.58 g, 13.2 mmol, 76%). The two geometrical isomers were inseparable by column chromatography and could only be purified by subjecting the **13/14** mixture to semi-preparative normal phase HLPC in 9:1 hexane/EtOAc.

3.9.1. Ethyl rhinocerotinoate (13). Oil; $[\alpha]_D^{26}$=+34 (c 1.95); IR ν_{max} 2931, 2863, 1715, 1662, 1608, 1463, 1330, 1222, 1147, 1036 cm^{-1}; ^1H NMR δ 5.69 (1H, br d, J=0.9 Hz, H-14), 4.14 (2H, q, J=7.1 Hz, 15-OCH_2CH$_3$), 2.49 (1H, dd, J=17.6, 3.7 Hz, H-6a), 2.34 (1H, m, J=17.6 Hz, H-6b), 2.32 (2H, m, H_2-11), 2.24 (2H, m, H_2-12), 2.21 (3H, d, J=0.9 Hz, H_3-16), 1.90 (1H, br d, J=12.2 Hz, H-1a), 1.75 (3H, s, H_3-17), 1.69 (1H, dd, J=8.6, 3.6 Hz, H-2a), 1.66 (1H, m, J=6.5 Hz, H-5), 1.60 (1H, m, J=3.6 Hz, H-2b), 1.47 (1H, br d, J=13.3 Hz, H-3a), 1.37 (1H, td, J=12.3, 3.8 Hz, H-1b), 1.27 (3H, t, J=7.2 Hz, 15-OCH$_2$CH_3), 1.19 (1H, dd, J=13.4, 4.2 Hz, H-3b), 1.07 (3H, s, H_3-20), 0.90 (3H, s, H_3-19), 0.87 (3H, s, H_3-18); ^{13}C NMR δ 200.0 (s, C-7), 166.6 (s, C-9), 166.3 (s, C-15), 158.4 (s, C-13), 130.5 (s, C-8), 115.9 (d, C-14), 49.6 (t, 15-OCH$_2$CH$_3$), 50.3 (d, C-5), 41.3 (t, C-3), 41.0 (s, C-10), 39.6 (t, C-12), 35.9 (t, C-1), 35.2 (t, C-6), 33.1 (s, C-4), 32.5 (q, C-18), 27.7 (t, C-11), 21.3 (q, C-19), 18.8 (q, C-16), 18.6 (t, C-2), 18.2 (q, C-20), 14.3 (q, 15-OCH$_2$CH$_3$), 11.4 (q, C-17); EIMS m/z (rel. int.) 346 [M^+] (42), 331 (12), 318 (32), 300 (54), 285 (31), 258 (67), 245 (30), 205 (37), 161 (21), 135 (100); HRFABMS obsd 347.2586 [(M+H)$^+$], $C_{22}H_{35}O_3$ requires 347.2586.

3.9.2. Ethyl isorhinocerotinoate (14). Oil; $[\alpha]_D^{26}$=+47 (c 0.48); IR ν_{max} 2931, 2863, 1714, 1662, 1603, 1444, 1377, 1165, 1144, 1036 cm^{-1}; ^1H NMR δ 5.67 (1H, br d,

J=1.1 Hz, H-14), 4.14 (2H, q, J=7.1 Hz, 15-OCH_2CH$_3$), 2.75 (2H, m, H$_2$-12), 2.49 (1H, dd, J=17.5, 3.8 Hz, H-6a), 2.35 (1H, dd, J=17.6, 14.1 Hz, H-6b), 2.34 (2H, m, H$_2$-11), 2.05 (1H, br d, J=12.4 Hz, H-1a), 1.94 (3H, d, J=1.3 Hz, H$_3$-16), 1.84 (3H, s, H$_3$-17), 1.71 (1H, dd, J=14.2, 3.9 Hz, H-5), 1.69 (1H, m, H-2a), 1.62 (1H, tt, J=12.1, 3.6 Hz, H-2b), 1.47 (1H, br d, J=13.4 Hz, H-3a), 1.42 (1H, td, J=12.6, 3.9 Hz, H-1b), 1.26 (3H, t, J=7.1 Hz, 15-OCH$_2$CH_3), 1.23 (1H, td, J=13.3, 4.1 Hz, H-3b), 1.10 (3H, s, H$_3$-20), 0.91 (3H, s, H$_3$-19), 0.88 (3H, s, H$_3$-18); ^{13}C NMR δ 200.3 (s, C-7), 167.2 (s, C-9), 166.0 (s, C-15), 157.9 (s, C-13), 130.6 (s, C-8), 117.0 (d, C-14), 59.6 (t, 15-OCH_2CH$_3$), 50.2 (d, C-5), 41.3 (t, C-3), 41.1 (s, C-10), 35.9 (t, C-1), 35.3 (t, C-6), 33.1 (s, C-4), 32.5 (q, C-18), 32.2 (t, C-12), 27.6 (t, C-11), 24.9 (q, C-16), 21.3 (q, C-19), 18.7 (t, C-2), 18.3 (q, C-20), 14.3 (q, 15-OCH$_2$$CH_3$), 11.3 (q, C-17); EIMS m/z (rel. int.) 346 [M$^+$] (37), 301 (18), 285 (22), 258 (39), 220 (50), 205 (57), 176 (33), 135 (92), 127 (100); HRFABMS obsd 347.2587 [(M+H)$^+$] $C_{22}H_{35}O_3$ requires 347.2586.

3.10. Preparation of (+)-14,15-bisnorlabda-8-en-7,13-dione (15)

Treatment of (+)-14,15-bisnorlabda-8-en-13-one (**8**, 4.98 g, 19.0 mmol) with CrO_3 (28.5 g, 285 mmol, 15 equiv.) and pyridine (46.0 mL, 570 mmol, 30 equiv.) as described in Section 3.8 gave a brown oil (4.53 g). Flash chromatography of the crude product in 7:3 hexane/EtOAc afforded (+)-14,15-bisnorlabda-8-en-7,13-dione (**15**) as a colorless oil (4.26 g, 15.4 mmol, 81%) which could be crystallized from cold hexane to give large white needles. A small amount of starting material (**8**, 156 mg, 3%) was also recovered from the column.

3.10.1. (+)-14,15-Bisnorlabda-8-en-7,13-dione (15). White solid; mp 78–80°C, lit.[24] 79.5–80.5°C; $[\alpha]_D^{26}$=+58 (c 1.89), lit.[24] +64.5°; IR ν_{max} 2931, 2870, 1716, 1661, 1607, 1417, 1366, 1330, 1162, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (2H, m, H$_2$-12), 2.51 (1H, m, H-6a), 2.46 (2H, m, H$_2$-11), 2.34 (1H, dd, J=17.5, 14.3 Hz, H-16), 2.17 (3H, s, H$_3$-16), 1.88 (1H, br d, J=12.4 Hz, H-1a), 1.70 (1H, m, H-2a), 1.71 (3H, s, H$_3$-17), 1.67 (1H, dd, J=14.2, 3.6 Hz, H-5), 1.57 (1H, m, H-2b), 1.47 (1H, br d, J=13.4 Hz, H-3a), 1.25 (1H, td, J=12.6, 3.7 Hz, H-1b), 1.23 (1H, td, J=13.4, 4.1 Hz, H-3b), 1.08 (3H, s, H$_3$-20), 0.91 (3H, s, H$_3$-19), 0.87 (3H, s, H$_3$-18); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.8 (s, C-13), 199.9 (s, C-7), 166.7 (s, C-9), 130.4 (s, C-8), 50.4 (d, C-5), 42.4 (t, C-12), 41.3 (t, C-3), 41.1 (s, C-10), 35.9 (t, C-1), 35.2 (t, C-6), 33.1 (s, C-4), 32.5 (q, C-18), 29.8 (q, C-16), 22.7 (t, C-11), 21.3 (q, C-19), 18.5 (t, C-2), 17.9 (q, C-20), 11.3 (q, C-17); EIMS m/z (rel. int.) 276 [M$^+$] (13), 258 (7), 233 (37), 215 (11), 205 (41), 136 (24), 135 (100), 107 (12), 91 (17); HRFABMS obsd 277.2167 [(M+H)$^+$], $C_{18}H_{29}O_2$ requires 277.2168.

3.11. Horner–Wadsworth–Emmons reaction of (+)-14,15-bisnorlabda-8-en-17,13-dione (15)

NaH (336 mg, 14.0 mmol, 1.2 equiv.) was stirred in anhydrous THF (15.0 mL), whilst triethyl phosphonoacetate (2.78 mL, 14.0 mmol, 1.2 equiv.) in anhydrous THF (5.0 mL) was added dropwise at room temperature. The resulting solution was stirred at room temperature for 30 min then the dione **15** (3.22 g, 11.7 mmol) in anhydrous THF (20 mL) was added dropwise and the reaction mixture stirred at ambient temperature overnight. The reaction mixture was concentrated in vacuo and taken up in Et_2O (50 mL), washed with H_2O (3×10 mL), dried ($MgSO_4$) and concentrated to give a light yellow oil (6.91 g). Silica gel flash chromatography (7:3 hexane/EtOAc) of the oil yielded a mixture of ethyl rhinocerotinoate (**13**) and ethyl isorhinocerotinoate (**14**) as a colorless oil (3.87 g, 11.2 mmol, 96%). ^{1}H NMR spectroscopy of the **13/14** mixture indicated that it was composed of a 10:1 mixture of **13/14**.

3.12. Saponification of esterified 7-oxolabda-8,13-dien-15-oic acid derivatives

The 10:1 **13/14** mixture (3.40 g, 9.83 mmol) and 5 M KOH (10 mL, 50 mmol, 5.1 equiv.) were refluxed in EtOH (40 mL) for 6 h. The reaction mixture was then concentrated in vacuo to give a cloudy aqueous solution (15 mL), which was acidified with 1 M HCl and extracted with $CHCl_3$ (3×25 mL). The organic fractions were combined, dried and concentrated to give a 12:3:2 mixture (determined by ^{1}H NMR spectroscopy) of rhinocerotinoic acid (**1**), isorhinocerotinoic acid (**5**) and (+)-7-oxolabda-8,13(16)-dien-15-oic acid (**16**) as a colourless oil (2.98 g, 9.37 mmol, 95%). Trituration of this oil with hexane and vacuum sublimation (150°C, 0.5 mm Hg) of the resulting off-white solid allowed the isolation of isomerically pure (by ^{1}H NMR spectroscopy) **1** (1.01 g, 48% of the total **1** in the mixture) as fine white crystals. The oil obtained from the mother-liquor was similarly treated with cold MeOH/water (10:1) to yield isomerically pure **5** (47 mg, 9% of the total **5** in the mixture). The mother-liquors from the second crystallization were combined to give a 3.11:1.37:1 (approximately 6:3:2, estimated from ^{1}H NMR spectroscopy) mixture of **1/5/16** as an oil (1.91 g, 6.01 mmol) that was inseparable by both normal phase and reversed phase HPLC. The acid **16** could therefore not be obtained pure and was isolated as the methyl ester **19** as described below.

The 6:3:2 **1/5/16** (1.91 g, 6.01 mmol) mixture was dissolved in MeOH (10 mL) and treated with an ethereal diazomethane solution (20 mL, approximately 34 mmol, 5.7 equiv.)[37] at 0°C. The bright yellow solution was allowed to stand in ice for 30 min and excess diazomethane removed by evaporation. The residual MeOH solution was concentrated in vacuo to give a mixture of the methyl esters **17**–**19** in the same ratio of 6:3:2 as a light yellow oil (1.99 g, 5.99 mmol, 100%). A portion of the methylated mixture (1.69 g) was purified by repeated flash chromatography in 19:1 and 9:1 hexane/EtOAc and normal phase HPLC of mixed fractions in 17:3 hexane/EtOAc to yield methyl rhinocerotinoate (**17**, 0.68 g), methyl isorhinocerotinoate (**18**, 0.34 g) and methyl 7-oxolabda-8,13(16)-dien-15-oate (**19**, 0.19 g) as colorless oils. It should be noted that the masses of the methyl esters isolated are not representative of their yields due to the losses incurred through the extensive chromatography required to separate these isomers.

The 2:1 **13/14** mixture (5.82 g, 16.8 mmol; prepared by $POCl_3$ dehydration) was treated in the same manner to give

a 10:5:2 mixture (determined by ^{1}H NMR spectroscopy) of rhinocerotinoic acid (**1**), isorhinocerotinoic acid (**5**) and (+)-7-oxolabda-8,13(16)-dien-15-oic acid (**16**) as an orange semi-solid residue (5.01 g, 15.8 mmol, 94%). The mixture was taken up in hexane (60 mL) and stored overnight at 0°C when an off white solid (2.03 g) precipitated from solution. The solid was vacuum sublimed (150°C, 0.5 mm Hg) to give isomerically pure **1** as white needles (1.81 g, 61% of the total **1** in the reaction mixture). The mother-liquor from the crystallization was discarded.

The 10:1 **13/14** mixture (20 mg, 0.06 mmol) and K_2CO_3 (41 mg, 0.30 mmol, 5.0 equiv.) was refluxed for 14 h in EtOH (4.0 mL) and H_2O (1.0 mL). Work-up of the reaction in the usual manner gave a 7:2:7 mixture (determined by ^{1}H NMR spectroscopy) of rhinocerotinoic acid (**1**), isorhinocerotinoic acid (**5**) and (+)-7-oxolabda-8,13(16)-dien-15-oic acid (**16**) as a colorless oil (16.3 mg, 0.05 mmol, 83%).

3.12.1. Rhinocerotinoic acid (1). Fine white needles; mp 189–190°C, lit.[2] 189–190°C; $[\alpha]_D^{27}$=+40 (*c* 2.52), lit.[2] +42; IR ν_{max} 3145 (br), 2931, 2853, 1745, 1694, 1657, 1630, 1596, 1436, 1338, 1219, 1146 cm^{-1};^{1}H and ^{13}C NMR data identical to published values;[2] EIMS *m/z* (rel. int.) 318 [M$^+$] (24), 300 (26), 290 (32), 258 (31), 231 (19), 205 (54), 177 (23), 135 (100), 121 (29); HRFABMS obsd 319.2272 [(M+H)$^+$], $C_{20}H_{31}O_3$ requires 319.2273.

3.12.2. Isorhinocerotinoic acid (5). White crystalline solid; mp 155–157°C, lit.[2] 156–158°C; $[\alpha]_D^{27}$=+50 (*c* 1.26), lit.[2] +54; IR ν_{max} 3214 (br), 2931, 2863, 1693, 1651, 1634, 1592, 1442, 1384, 1254, 1164, 1002 cm^{-1}; ^{1}H and ^{13}C NMR identical to published values;[2] EIMS *m/z* (rel. int.) 318 [M$^+$] (24), 300 (10), 285 (13), 258 (22), 241 (9), 220 (45), 205 (44), 176 (22), 135 (100); HRFABMS obsd 319.2273 [(M+H)$^+$], $C_{20}H_{31}O_3$ requires 319.2273.

3.12.3. Methyl rhinocerotinoate (17). Oil; $[\alpha]_D^{27}$=+43 (*c* 1.65, $CHCl_3$); IR ν_{max} 2947, 2930, 2863, 1721, 1663, 1607, 1435, 1223, 1150, 1013 cm^{-1}; ^{1}H NMR δ 5.71 (1H, d, *J*=1.2 Hz, H-14), 3.69 (3H, s, 15-OMe), 2.49 (1H, dd, *J*=17.6, 3.7 Hz, H-6a), 2.37 (1H, m, *J*=17.6 Hz, H-6b), 2.31 (2H, m, H_2-11), 2.24 (2H, m, H_2-12), 2.21 (3H, d, *J*=1.3 Hz, H_3-16), 1.90 (1H, br d, *J*=12.7 Hz, H-1a), 1.76 (3H, s, H_3-17), 1.69 (1H, dd, *J*=14.3, 3.7 Hz, H-5), 1.65 (1H, m, H-2a), 1.59 (1H, m, H-2b), 1.47 (1H, br d, *J*=13.2 Hz, H-3a), 1.35 (1H, td, *J*=12.7, 3.7 Hz, H-1b), 1.21 (1H, td, *J*=13.5, 4.1 Hz, H-3b), 1.08 (3H, s, H_3-20), 0.91 (3H, s, H_3-19), 0.87 (3H, s, H_3-18); ^{13}C NMR δ 200.0 (s, C-7), 167.0 (s, C-15), 166.3 (s, C-9), 158.9 (s, C-13), 130.5 (s, C-8), 115.5 (d, C-14), 50.9 (q, 15-OMe), 50.3 (d, C-5), 41.3 (t, C-3), 41.0 (s, C-10), 39.6 (t, C-12), 35.9 (t, C-1), 35.2 (t, C-6), 33.1 (s, C-4), 32.5 (q, C-18), 27.7 (t, C-11), 21.3 (q, C-19), 18.8 (q, C-16), 18.6 (t, C-2), 18.2 (q, C-20), 11.4 (q, C-17); EIMS *m/z* (rel. int.) 332 [M$^+$] (69), 317 (26), 304 (43), 300 (35), 285 (36), 258 (28), 245 (28), 205 (25), 135 (100), 121 (24); HRFABMS obsd 333.2420 [(M+H)$^+$], $C_{21}H_{33}O_3$ requires 333.2430.

3.12.4. Methyl isorhinocerotinoate (18). Oil; $[\alpha]_D^{27}$=+49 (*c* 1.76, $CHCl_3$); IR ν_{max} 2948, 2931, 2862, 1718, 1662, 1606, 1440, 1166, 1145, 1022 cm^{-1}; ^{1}H NMR δ 5.68 (1H, br s, H-14), 3.68 (3H, s, 15-OMe), 2.74 (2H, m, H_2-12), 2.49 (1H, dd, *J*=17.5, 3.8 Hz, H-6a), 2.35 (1H, dd, *J*=17.3, 14.6 Hz, H-6b), 2.32 (2H, m, H_2-11), 2.06 (1H, br d, *J*=12.3 Hz, H-1a), 1.95 (3H, d, *J*=1.0 Hz, H_3-16), 1.84 (3H, s, H_3-17), 1.71 (1H, dd, *J*=14.1, 3.7 Hz, H-5), 1.69 (1H, m, H-2a), 1.63 (1H, tt, *J*=11.1, 3.5 Hz, H-2b), 1.47 (1H, br d, *J*=13.3 Hz, H-3a), 1.42 (1H, td, *J*=12.6, 3.8 Hz, H-1b), 1.23 (1H, td, *J*=13.2, 4.2 Hz, H-3b), 1.10 (3H, s, H_3-20), 0.91 (3H, s, H_3-19), 0.88 (3H, s, H_3-18); ^{13}C NMR δ 200.3 (s, C-7), 167.1 (s, C-9), 166.4 (s, C-15), 158.4 (s, C-13), 130.6 (s, C-8), 116.5 (d, C-14), 51.0 (q, 15-OMe), 50.2 (d, C-5), 41.3 (t, C-3), 41.1 (s, C-10), 35.9 (t, C-1), 35.3 (t, C-6), 33.1 (s, C-4), 32.5 (q, C-18), 32.3 (t, C-12), 27.6 (t, C-11), 25.0 (q, C-16), 21.3 (q, C-19), 18.7 (t, C-2), 18.2 (q, C-20), 11.3 (q, C-17); EIMS *m/z* (rel. int.) 332 [M$^+$] (45), 300 (15), 285 (26), 258 (35), 220 (55), 205 (28), 161 (39), 135 (100), 113 (58), 91 (38); HRFABMS obsd 333.2430 [(M+H)$^+$], $C_{21}H_{33}O_3$ requires 333.2430.

3.12.5. Methyl 7-oxolabda-8,13(16)-dien-15-oate (19). Oil; $[\alpha]_D^{27}$=+57 (*c* 3.03); IR ν_{max} 2951, 2931, 2870, 1742, 1662, 1607, 1435, 1332, 1154, 1017 cm^{-1}; ^{1}H and ^{13}C NMR data see Table 1; EIMS *m/z* (rel. int.) 332 [M$^+$] (100), 317 (53), 299 (11), 285 (27), 259 (24), 243 (13), 231 (44), 205 (13), 135 (79), 91 (25); HRFABMS obsd 333.2420 [(M+H)$^+$], $C_{21}H_{33}O_3$ requires 333.2430.

3.13. Acid hydrolysis of the 10:1 ethyl rhinocerotinoate (13)/ethyl isorhinocerotinoate (14) mixture (prepared via the HWE reaction)

The 10:1 **13/14** mixture (719 mg, 2.08 mmol) and 5 M H_2SO_4 (6.0 mL) in AcOH (7.5 mL) was heated at 100°C for 4 h. The reaction mixture was diluted with H_2O (50 mL), extracted with EtOAc (2×15 mL) and the combined organic fractions extracted with 10% K_2CO_3 (6×10 mL). The aqueous phases were combined, acidified with HCl and extracted with EtOAc (3×15 mL). The combined acidic organic phases were washed with H_2O (5 mL), dried (Na_2SO_4) and concentrated to give a mixture of **1** and **5** in a ratio of 10:1 (determined by ^{1}H NMR spectroscopy) as a light yellow solid (542 mg, 1.70 mmol, 82%). Washing with hexane and vacuum sublimation (150°C, 0.5 mm Hg) afforded rhinocerotinoic acid (**1**, 478 mg, 1.50 mmol, 72% overall) as fine white needles (isomerically pure by ^{1}H NMR).

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