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Synthetic studies towards picrasane quassinoids

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Abstract—An advanced intermediate **40** with the ABC ring of the picrasane quassinoid skeleton has been synthesised from *ent*-halimic acid. The bicyclic system of the starting material has been incorporated as the BC part of the ABC system. Until date, no diterpenes of the antipode series have been used in this kind of approach.

1. Introduction

The quassinoids[1] are a wide group of natural products mainly isolated from *Simaroubaceae*[2] that show interesting biological activities. They possess many different skeletons, although the most usual is the picrasane one. These compounds are generally δ-lactones, highly oxygenated tetra or pentacyclics[3] with many stereogenic centres, making them very interesting compounds from the synthetic point of view.[4] In general, the picrasane skeleton shows an interannular ring junction *trans* between rings A and B although some *cis* junctions can be observed as in javanicoside A[5] (Fig. 1).

The interest for these terpenoids starts with bruceantin,[6] isolated for the first time from *Brucea antidysenterica*, an Ethiopia tree used for cancer treatment. Bruceantin shows activity in mice against colon 38 and L1210, B16 melanoma and P388 leukaemia, as well as for other biological activities.[7]

Until date, many synthetic approaches have been communicated for the preparation of the ABC,[8] BCD,[9] BCE,[10] BCDE,[11] ABCD,[12] ABCDE[13] ring systems with several natural products used as starting materials for the preparation, including androgens,[14] bile acids[15] and more recently communic acid diterpenes.[16] At this respect, the contribution of Grieco et al. is mentionable who have achieved the synthesis of several tetra and pentacyclic quassinoids[17] and (±)-bruceantin.[18]

In this paper, we disclose a new approach to the picrasane skeleton, in particular to the ABC tricyclic system of intermediate **5** (Scheme 1) amenable for further elaboration into target picrasane skeleton by rearrangement of Me-18 and final lactonization.

ent-Halimic **1** is an excellent precursor for quassinoids with picrasane skeleton, as its biannular system could be incorporated as the BC rings of the picrasane, keeping the relative and absolute configuration in C-4 and C-5 (C-9 and C-10 in quassinoids with this skeleton) (Scheme 1).

Scheme 1 shows the retrosynthesis for picrasanes as **6** that could proceed by rearrangement of Me-18 of *abeo*picrasanes as **5**. This kind of transformation has been achieved in analogues as the *ent*-halimane **7** transformed into the *ent*-labdane **8**[19] using $BF_3 \cdot Et_2O$ as shown in Scheme 3.

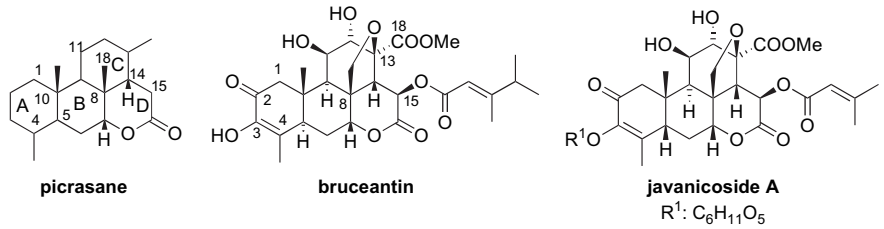

Figure 1.

Keywords: Quassinoids; Picrasane; Triterpenes; *ent*-Halimic acid.
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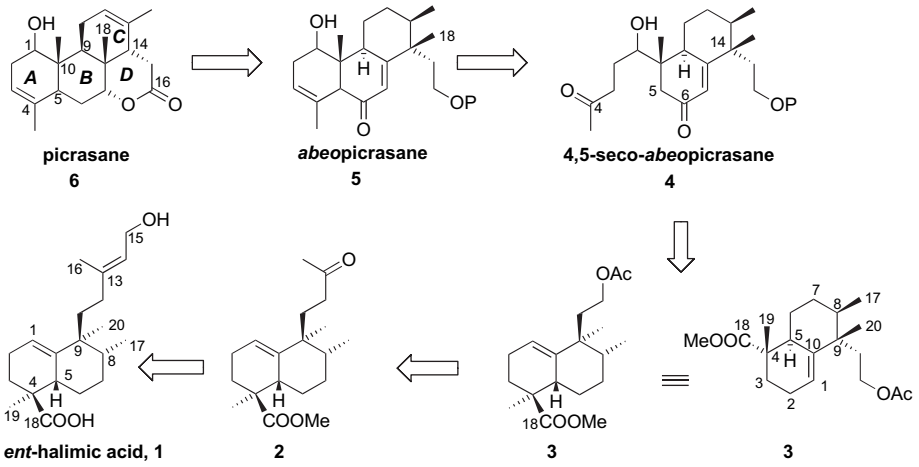


Scheme 1.

The strategy will follow with ring A formation (Scheme 1) using the carbonyl on C-6 with C-5 behaving as nucleophile. It will be necessary to have 4,5-seco-*abeo*picrasane as **4** that could be synthesised from the tetranorderivative **3**, and this compound from the methylketone **2** a derivative of *ent*-halimic **1** acid, previously used as starting material for the synthesis of many biological active natural products such as *ent*-halimanolides,[20] chettaphanin I and II,[21] analogues of disydiolyde as 15-epicladocoran A and B[22] and terpenoalcaloids as agelasine C.[23]

The most important structural feature of **4** is the α,β-unsaturated carbonyl group necessary for the nucleophile behaviour of C-5 (C-3 in the *ent*-halimane skeleton) and ring A formation.

For the synthesis of ring A, it will be necessary as well to introduce at C-18 of **3**, a side chain with an electrophilic group in the right position to achieve the condensation with C-3 in **3** or C-5 in **4**. The synthon should have too, the side chain in C-14 of the adequate size for ring D formation of the picrasane skeleton.

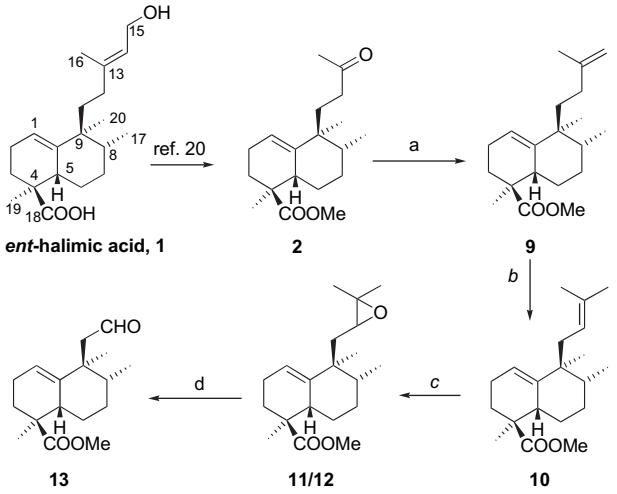
So four sections are provided for the synthesis of *abeo*picrasanes from *ent*-halimic acid **1**.

1. Side chain degradation.
2. Alkylation at C-18 and synthesis of the α,β-unsaturated carbonyl group.
3. Ring A formation.
4. Studies in the functionality required for picrasanes ring D formation.

1.1. Side chain degradation

The side chain degradation of **2**[21] without changing $\Delta^{1(10)}$ olefin has been achieved using the methodology recently developed by us[24] (Scheme 2).

Wittig[25] reaction of CH_3PPh_3Br and NaHMDS with ketone **2** gives **9** that by refluxing two hours with *p*-TsOH/C_6H_6 gave **10**, being produced by a chemoselective isomerisation of the double bond of the side chain. Treatment of **10** with 1 mol of *m*-CPBA produces epoxides **11/12** chemoselectively. Oxidation of the **11/12** mixtures was done with H_5IO_6 to give **13** (Scheme 2).

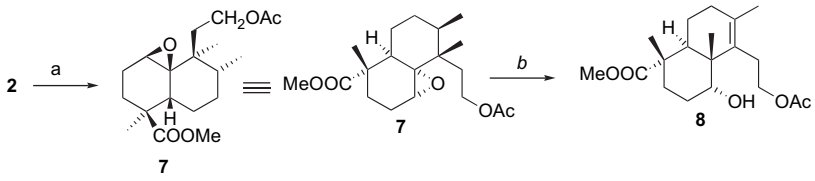


Scheme 2. Reagents and conditions: (a) CH_3PPh_3Br, NaHMDS, −78 °C, 2 h, (96%); (b) *p*-TsOH, C_6H_6, 60 °C, 2 h, (91%); (c) *m*-CPBA, CH_2Cl_2, rt, 45 min, (82%); (d) H_5IO_6, THF, rt, 1 h, (80%).

At this stage, we decided to test the possibility of Me-20 rearrangement that will transform an *ent*-halimane into an *ent*-labdane skeleton, necessary for the transformation of *abeo*picrasanes into picrasanes. Reaction of **2** with UHP/ATFA[26] gave the epoxytetranorderivative **7** in an excellent yield and diastereoselection. Reaction of **7** with $F_3B{\cdot}Et_2O$ gave the *ent*-labdane **8** in moderate yield (Scheme 3). In this manner, the *ent*-halimane skeleton is transformed into an *ent*-labdane following the reverse to the biosynthetic pathway, this rearrangement being described for the first time. This rearrangement will be used for the transformation of tricyclic *abeo*picrasane derivatives into compounds with picrasane skeleton in due course.

1.2. Alkylation on C-18 and synthesis of the α,β-unsaturated carbonyl group

Once the side chain has been adequately reduced, we followed the designed strategy.



Scheme 3. Reagents and conditions: (a) UHP, TFAA, CH_2Cl_2, 0 °C, 1 h, (95%); (b) $BF_3{\cdot}Et_2O$, C_6H_6, rt, 2 h, (43%).

The necessary alkylation at C-18 for ring A formation of the picrasanes needs to have in account several significant factors.

First of all, it is necessary to say that an oxygenated functionality at C-1 (C-18 of the *ent*-halimane skeleton) is present in several biological active quassinoids with picrasane skeleton,[1] that is the reason to alkylate C-18 by addition reaction to an aldehyde.

Secondly, it is necessary to consider that the fragment to be used in the reaction should have four carbon atoms as shown in the retrosynthetic scheme (Scheme 1), and to have an electrophilic group in the adequate position for ring A formation. For this reason, 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane was chosen to achieve this objective.

The synthesis of **18** from **13** is shown in Scheme 4. Reduction of **13** with $NaBH_4$ gave the hydroxyderivative **14** that after protection as its silyl derivative **15** was reduced with $LiAlH_4$ to give **16**. TPAP[27] oxidation of **16** lead to the unstable aldehyde **17**. Addition of the magnesium derivative of 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane generated 'in situ' to **17** gave **18**[28] in an excellent 93% yield (Scheme 4).

The secopicrasane **18** is a mixture of the two alcohols in C-1, which were very difficult to separate by column chromatography. Deprotection of **18** with TBAF[29] gave diols **19** and **20** readily separated by column chromatography (Scheme 5). Acetylation of **19** and **20** with Ac_2O/Py gave the diacetates **21** and **22**, respectively, which by treatment in acidic conditions produce **23** and **24**, respectively.

Compounds **23** and **24** are adequate to obtain the desired 4,5-seco-*abeo*picrasanes with an α,β-unsaturated carbonyl group. Treatment of **23** and **24** with Na_2CrO_4 gave **25** and **26**, respectively (Scheme 5). From the signal at 5.89 ppm of the olefinic hydrogen at C-7 for **25** and **26** in their ^1H NMR spectra, the presence of the α,β-unsaturated carbonyl group was deduced.

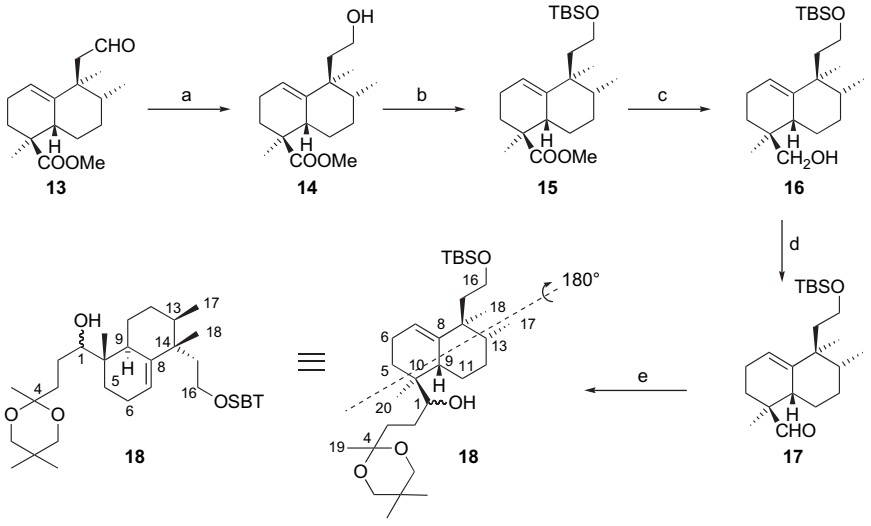
1.3. Ring A formation

Once that we have the α,β-unsaturated system in the ring and the side chain on C-18, it is time to form the ring A.

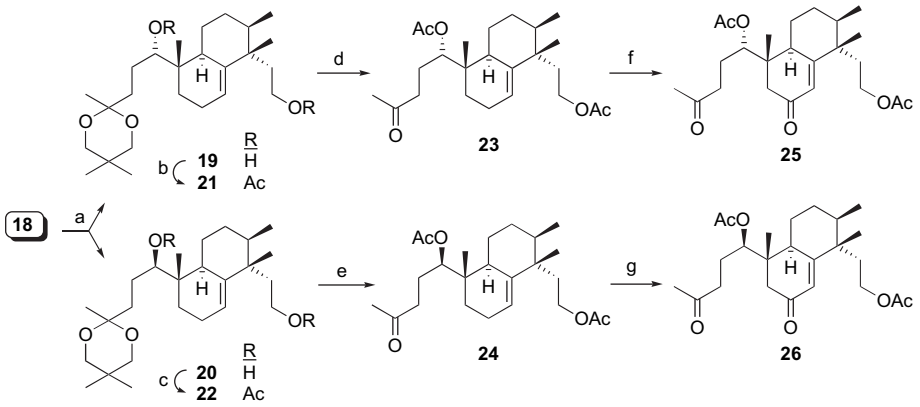
First of all, the aldol condensation[30] was tried in different conditions for each of the isomers **25** and **26**. In Scheme 6 and Table 1, the results obtained for **25** are shown that after treatment with different bases give compounds **27**, **28**, **29** and/or **30**.

Compound **28** is the result of the desired condensation, that is, addition of the α′ enolate of the enone to the carbonyl at C-4. In structure **28**, the α,β-unsaturated carbonyl group remains unalterated (^1H NMR: 6.12 ppm, H-7), and a correlation between H-5 with C-3 and the quaternary carbon at C-4 in the $^1H/^{13}C$ (HMBC) corroborates that the condensation has taken place as indicated.

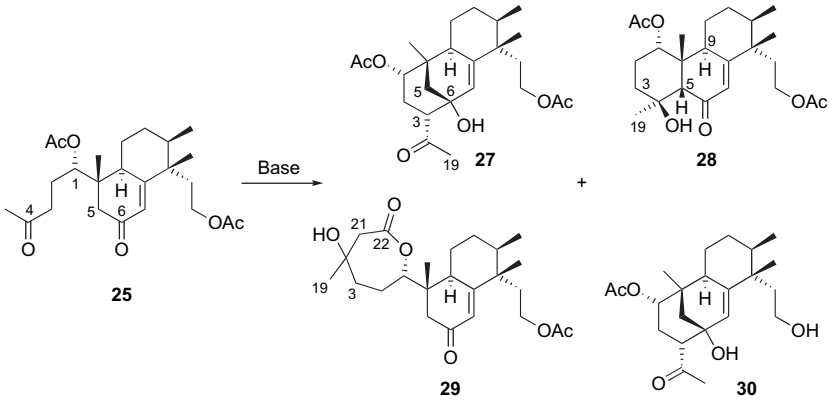
The configuration of the two new stereogenic centres in **28** was established by NOE experiments. In the ROESY experiment, a NOE between Me-19 and H-9 can be observed (Fig. 2). As C-9 configuration is known, the presence of



Scheme 4. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to rt, 15 min, (91%); (b) TBDMSCl, DMF, 0 °C to rt, 18 h, (98%); (c) $LiAlH_4$, Et_2O, 0 °C to rt, 30 min, (98%); (d) TPAP, NMO, sieves, CH_2Cl_2, rt, 1 h, (91%); (e) 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane, THF, Mg, 35 °C, 30 min, then 0 °C to rt, 45 min (93%).



Scheme 5. Reagents and conditions: (a) TBAF, THF, rt, 90 min [**19** (56%), **20** (22%)]; (b) Ac_2O, Py, rt, 12 h (81%); (c) Ac_2O, Py, rt, 16 h (83%); (d) *p*-TsOH, acetone, rt, 35 min (98%); (e) *p*-TsOH, acetone, rt, 45 min (94%); (f) Na_2CrO_4, Ac_2O, AcOH, NaOAc, 60 °C, 22 h (67%); (g) Na_2CrO_4, Ac_2O, AcOH, NaOAc, 60 °C, 24 h (52%).



Scheme 6.

Table 1. Different bases used in the treatment of **25** and compounds and yields obtained

Base	Temperature (°C)	**27** (%)	**28** (%)	**29** (%)	**30** (%)
KHMDS	−78	18	50	16	—
KHMDS	−100	12	35	31	—
LDA	−78	—	30	—	—
K_2CO_3/MeOH 1%	0	50	—	—	49

that NOE permits to establish as *cis* the junction of rings A and B and the *cis*-esteroid conformation, as is the only one where that effect appears. For the same reason, the C-4 configuration as *S*, being the hydroxy group β is established.

Once obtained the tricyclic compound **28** the configuration of the acetoxy group on ring A was established as equatorial by the coupling constants of the geminal hydrogen. This configuration was corroborated by the NOE between H-1 geminal to the acetoxy group with H-5 and Me-20 (Fig. 2). In this manner, all the configurations in that centre for all compounds with a secopicrasane skeleton are established.

Compound **27** is a tricyclic derivative formed by the addition of C-3 to the carbonyl at C-6. In the $^1H/^{13}C$ (HMBC) of **27** a correlation between H-3 with C-5 and C-6 indicates that the condensation has taken place as indicated. The new ring can only be formed from the α side of the bicyclic system. The coupling constants of H-1 and H-3 indicate that these hydrogens are axial and the presence of a NOE between them corroborates that these hydrogens are β and *cis* (Fig. 2).

Compound **29** is a seven-membered ring formed by the addition of acetate enolate in C-1 to the carbonyl at C-4. The ring formation is showed by the correlation in the HMBC experiment between H-19 with C-3 and C-4 and

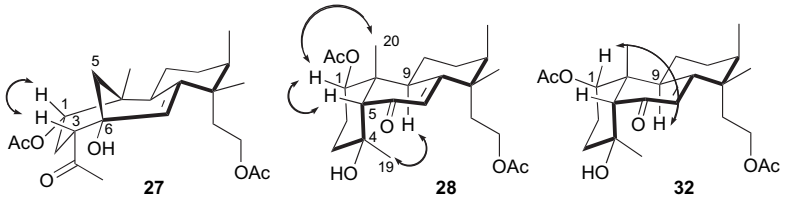
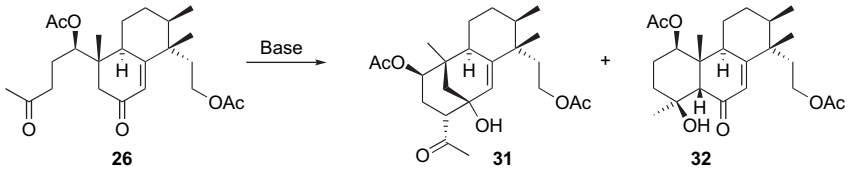


Figure 2.



Scheme 7.

with C-21. In some treatments with bases of **25** was obtained **30**, the product of partial hydrolysis of **27**.

As can be seen treatment of **25** with KHMDS at −78 °C gives **28** as major product, when the reaction is done at −100 °C, the yield of **29** increases and the yield of **27** decreases (Table 1).

When the cyclisation was done with LDA, only compound **28** was isolated in a 30% yield, but when using 1% K_2CO_3/MeOH, only compounds **27** and **30** in a 1:1 ratio were obtained due to the not desired condensation.

The aldol condensation of **26** was done by treatment of this compound with strong bases in different conditions (Scheme 7, Table 2), obtaining the condensation compounds **31** and **32**. The first one is the epimer at C-1 of **27**, being **32** the epimer of **28** at the same carbon atom.

In the ^{1}H NMR spectrum of **32**, the signal corresponding to the hydrogen geminal of the secondary acetoxy group appears at 5.14 ppm as a singlet, indicating that the hydrogen is equatorial and the configuration of the acetoxy group is β. The ROESY experiment shows a NOE (Fig. 2) between H-1 and H-9 corroborates H-1 as α.

In the reaction of **26** with KHMDS, the presence of compound **31** was detected but was impossible to isolate it, showing an increase in the yield of the condensation product **32** when the temperature decreased to −100 °C. When the reaction was carried out with LDA, only **32** was isolated in a 28% yield. As in the reaction with strong bases as LDA, there is no competence with other condensations, it was decided to carry out the reaction with a less bulky base as LDE[31] in order to favour the formation of **32**, but the yield did not increase.

Table 2. Different bases used in the treatment of **26** and compounds and yields obtained

Base	Temperature (°C)	**26** (%)	**31** (%)	**32** (%)
KHMDS	−78	9	Traces	14
KHMDS	−100	19	Traces	26
LDA	−78	—	—	28
LDE	−78	9	—	15

With these facts in mind, it looks reasonable that a good way to obtain the desired condensation for ring A formation in a picrasane skeleton will be to use these conditions in an analogue of **25** or **26** with a differently protected hydroxy group at C-1. In this manner, the acetoxy group participation will be avoided that lead to **29**, and the desired compound **28** will be obtained in a better yield.

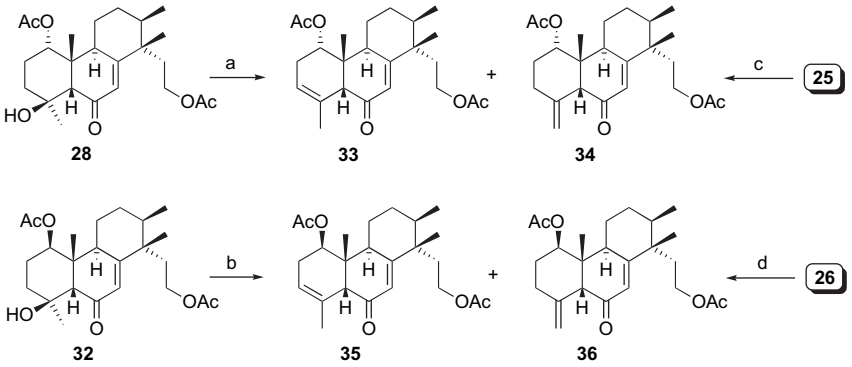
1.4. Studies in the functionality required for picrasanes ring D formation

Once obtained ring A, the next step is to eliminate the tertiary hydroxy group from the condensation products **28** and **32** in order to achieve the *abeo*picrasane structure. To do so, compounds **28** and **32** were treated with $SOCl_2$ as shown in Scheme 8.

Dehydration of **28** gives **33** and **34** and the same conditions with **32** gives **35** and **36** in a good yield. Compounds **33** and **35** have an *abeo*picrasane structure with a trisubstituted double bond in ring A, presents in many natural picrasanes.

The analysis of the ^{1}H NMR spectra of the crude mixtures for the reactions of **25** and **26** with bases tells us about the instability of the compounds obtained, as the yields after chromatography are a lot less as suggested by the ^{1}H NMR spectra.

In order to solve this problem, the intermediate compounds were not isolated doing the condensation and dehydration consecutively with **25** and **26** (Scheme 8). Addition of **25**



Scheme 8. Reagents and conditions: (a) $SOCl_2$, Py, 0 °C, 30 min [**33** (54%), **34** (36%)]; (b) $SOCl_2$, Py, 0 °C, 35 min [**35** (51%), **36** (34%)]; (c) (i) LDA, THF, −78 °C, 35 min, (ii) $SOCl_2$, Py, 0 °C, 15 min [**33** (13%), **34** (14%)]; (d) (i) LDA, THF, −78 °C, 30 min, (ii) $SOCl_2$, Py, 0 °C, 35 min [**35** (20%), **36** (8%)].

and **26** to LDA followed by treatment with $SOCl_2$ gives **33** and **34** and their epimers in C-1, **35** and **36**. When the reactions were done in this manner, the yield does not increase with respect of doing in two separate steps.

The next thing to do, to achieve our objectives, is to adequate the functionalization of **28** and **32** to obtain compounds that will lead to ring D formation in the picrasane skeleton. Several transformations were undertaken, the ones for **32** being shown in Scheme 9 and the ones for **28** in Scheme 10.

Treatment of **32** with *p*-TsOH gave the retroaldol product **26** (Scheme 9). This reaction, another trials with HI in different conditions indicate the difficulty inherent with the aldol group of **32**, which instead of elimination gives the retroaldol reaction.[32]

Attempt to epoxidate **32** in basic conditions with $^{t}BuOOH$[4,33] gave **38**, resulting from a retroaldol and ulterior condensation and isomerisation of the double bond (Scheme 9). Due to this instability, it is clear that for epoxidation these substrates should not contain the aldol group.

Treatment of **32** with $NaBH_4$ lead to the recovering of the starting material. If the reduction is done with $LiAlH_4$, tetraol **37** is obtained in good yield (Scheme 9). This compound looks suitable to try an electrophilic epoxidation for ring D of picrasane skeleton formation and rearrangement of Me-18.

Other substrates that could be adequate for trying nucleophilic epoxidation in ring B are **35** and **39**, the latter obtained by chemoselective hydrolysis of **35** (Scheme 9).

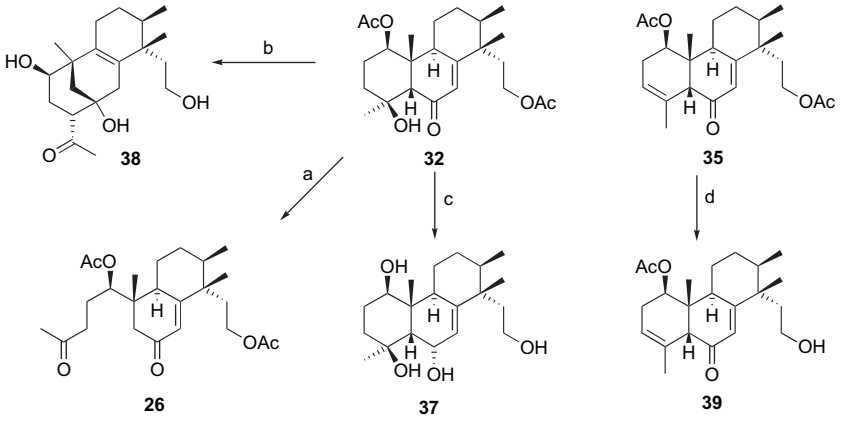
Reduction of **28** with $LiAlH_4$ gives tetraol **40**, this compound and its isomer in C-1, **37**, are adequate for ring D formation of picrasanes by epoxidation. The structure determination of **28** was done by study of the spectroscopy of its triacetoxiderivative **41** obtained by treatment of **40** with Ac_2O/Py. The presence of a NOE (Scheme 10) between Me-20 and H-6 establish that the acetoxy group in C-6 is α and so the stereochemistry at that centre for all the reduction compounds.

In this manner, we have obtained several compounds with the adequate functionalization, to obtain the required ring D of the picrasane skeleton.

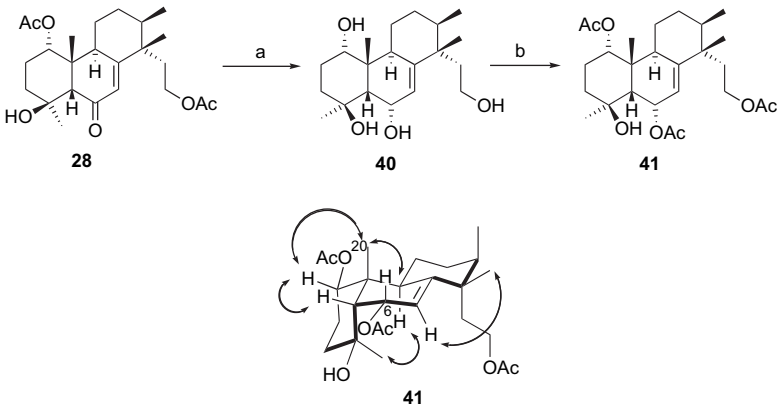
2. Conclusions

Starting with *ent*-halimic acid **1**, a bicyclic diterpene of the antipode series and a tricyclic intermediate of degradated triterpenes with picrasane skeleton have been obtained.

In this approach, the bicyclic system of the starting material has been incorporated as BC part of the ABC system synthesised. Until date, no diterpenes of the antipode series have been used in these kinds of approaches. Ring D formation of the picrasane skeleton will be tried in future, from



Scheme 9. Reagents and conditions: (a) *p*-TsOH, C_6H_6, 45 °C, 75 min (33%); (b) $^{t}BuOOH$, NaOH, 45 °C, 6 h (28%); (c) $LiAlH_4$, Et_2O, rt, 4 h (83%); (d) K_2CO_3, MeOH 1%, rt, 40 min (78%).



Scheme 10. Reagents and conditions: (a) $LiAlH_4$, Et_2O, rt, 15 h (83%); (b) Ac_2O, Py, rt, 3 days (73%).

oxygenated intermediates at C-6 as the ones synthesised in this paper or from deoxygenated compounds at C-6.

3. Experimental

3.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FTIR or an AVATAR 370 FTIR Thermo Nicolet spectrophotometers. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 and 77.0 ppm for ^{1}H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ (parts per million) and coupling constants (J) are given in hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as m/z (% rel. int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or fast atom bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionisation (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

3.2. Reaction of 2 with CH_3PPh_3Br/NaHMDS: 9

A 1.0 M solution of NaHMDS in THF (38.6 mL, 38.6 mmol) was added to a suspension of CH_3PPh_3Br (13.80 g, 38.7 mmol) in THF (100 mL) at −20 °C and under argon. The resulting mixture was allowed to warm to room temperature and the orange solution was stirred for 1 h, then cooled to −78 °C and the ketone **2** (1.2 g, 3.86 mmol) in THF (10 mL) was added. The mixture was again allowed to warm to room temperature and was stirred for additional 1 h. The reaction was quenched at −78 °C with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (hexane/EtOAc 95:5) to give **9** (1.1 g, 96%).

3.2.1. Methyl 15-nor-*ent*-halima-1(10),13-dien-18-oate (9). $[\alpha]_D^{22}$ +59.8 (*c* 1.0, $CHCl_3$); IR (film): 3090, 1732, 1451, 1379, 1258, 1196, 1163, 1113, 1022, 883, 804 cm^{-1}; ^{1}H NMR δ: 5.33 (1H, t, J=3.4 Hz, H-1), 4.68 (2H, br s, H-14), 3.64 (3H, s, –COOMe), 2.74–2.62 (1H, m, H-5), 1.73 (3H, s, Me-16), 2.16–1.19 (13H, m), 1.11 (3H, s, Me-19), 0.91 (3H, s, Me-20), 0.80 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 119.9 (C-1), 23.0 (C-2), 30.8 (C-3), 45.1 (C-4), 38.6 (C-5), 23.1 (C-6), 28.6 (C-7), 38.7 (C-8), 43.0 (C-9), 141.5 (C-10), 37.8 (C-11), 32.4 (C-12), 147.5 (C-13), 109.3 (C-14), 22.6 (C-16), 15.8 (C-17), 178.8 (C-18), 20.3 (C-19), 22.6 (C-20), 51.9 (–COO*Me*); EIMS: 304 (M^+, 7), 245 (36), 235 (93), 175 (100), 105 (24), 91 (13), 69 (12); EIHRMS: calcd for $C_{20}H_{32}O_2$ $(M)^+$ 304.2402, found $(M)^+$ 304.2411.

3.3. Isomerisation of 9: 10

To a solution of **9** (1.1 g, 3.46 mmol) in benzene (35 mL) *p*-toluenesulfonic acid (112 mg, 0.59 mmol) was added and the mixture was refluxed at 60 °C for 2 h. The solution was cooled to room temperature, extracted with Et_2O and the combined organic layers were successively washed with a 6% aqueous solution of $NaHCO_3$, water and brine. Drying (Na_2SO_4) and evaporation of the solvent provided **10** (961 mg, 91%).

3.3.1. Methyl 15-nor-*ent*-halima-1(10),12-dien-18-oate (10). $[\alpha]_D^{22}$ −15.4 (*c* 1.7, $CHCl_3$); IR (film): 1732, 1452, 1379, 1250, 1196, 1163, 1111 cm^{-1}; ^{1}H NMR δ: 5.32 (1H, s, H-1), 5.03–4.96 (1H, m, H-12), 3.65 (3H, s, –COOMe), 2.79–2.73 (1H, m, H-5), 2.15–1.96 (4H, m), 1.83–1.16 (7H, m), 1.62 and 1.60 (3H, s each, Me-14, Me-16), 1.11 (3H, s, Me-19), 0.86 (3H, s, Me-20), 0.79 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 121.8 (C-1), 22.9 (C-2), 31.2 (C-3), 45.2 (C-4), 38.1 (C-5), 23.0 (C-6), 28.7 (C-7), 38.7 (C-8), 43.8 (C-9), 141.7 (C-10), 38.0 (C-11), 119.5 (C-12), 132.1 (C-13), 18.3 (C-14), 19.6 (C-16), 15.8 (C-17), 178.9 (C-18), 16.3 (C-19), 26.3 (C-20), 51.9 (–COO*Me*); EIMS: 304 (M^+, 10), 235 (85), 175 (100), 105 (20), 69 (15); EIHRMS: calcd for $C_{20}H_{32}O_2$ $(M)^+$ 304.2402, found $(M)^+$ 304.2412.

3.4. Reaction of 10 with *m*-CPBA: 11 and 12

An ice-cooled solution of **10** (65 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) was treated with *m*-CPBA (37 mg, 0.21 mmol). The reaction mixture was stirred at room temperature for 45 min, then a 10% aqueous solution of Na_2SO_3 (10 mL) was added and stirred for additional 30 min. The mixture was extracted with EtOAc, washed with a 6% aqueous solution of $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4), evaporated and chromatographed on silica gel to yield two epimeric epoxides in a 1:1 ratio, **11** (28 mg, 41%) and **12** (28 mg, 41%).

3.4.1. Methyl 12,13*RorS*-epoxy-15-nor-*ent*-halim-1(10)-en-18-oate (11). $[\alpha]_D^{22}$ +32.2 (*c* 0.6, $CHCl_3$); IR (film): 1728, 1462, 1374, 1244, 1164, 1111 cm^{-1}; ^{1}H NMR δ: 5.47 (1H, s, H-1), 3.63 (3H, s, –COOMe), 2.72–2.60 (1H, m, H-5), 2.66 (1H, dd, J=7.6, 2.8 Hz, H-12), 2.29 (1H, d, J=14.6 Hz, H-11), 2.10–2.04 (2H, m, H-2), 2.01–1.95 (1H, m, H-7), 1.77 (1H, ddd, J=8.8, 6.4, 6.4 Hz, H-3), 1.66–1.63 (1H, m, H-8), 1.53–1.40 (2H, m, H-6), 1.52 (1H, ddd, J=8.8, 6.4, 6.4 Hz, H-3), 1.45–1.32 (1H, m, H-7), 1.35–1.25 (1H, m, H-11), 1.27 (6H, s, Me-14, Me-16), 1.12 (3H, s, Me-19), 1.05 (3H, s, Me-20), 0.82 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 120.4 (C-1), 22.8 (C-2), 30.5 (C-3), 44.9 (C-4), 38.3 (C-5), 22.9 (C-6), 28.5 (C-7), 38.9 (C-8), 43.0 (C-9), 140.9 (C-10), 38.1 (C-11), 61.7 (C-12), 56.9 (C-13), 19.2 (C-14), 24.8 (C-16), 15.3 (C-17), 178.5 (C-18), 19.9 (C-19), 23.0 (C-20), 51.7 (–COO*Me*); EIMS: 320 (M^+, 2), 243 (25), 234 (50), 103 (12), 175 (100), 105 (35), 85 (38); EIHRMS: calcd for $C_{20}H_{32}O_3$ $(M)^+$ 320.2351, found $(M)^+$ 320.2347.

3.4.2. Methyl 12,13*RorS*-epoxy-15-nor-*ent*-halim-1(10)-en-18-oate (12). $[\alpha]_D^{22}$ +18.6 (*c* 0.7, $CHCl_3$); IR (film): 1728, 1462, 1377, 1248, 1167, 1113 cm^{-1}; ^{1}H NMR δ: 5.39 (1H, t, J=3.7 Hz, H-1), 3.65 (3H, s, –COOMe), 2.90–2.78 (1H, m, H-5), 2.63 (1H, dd, J=8.3, 3.7 Hz, H-12), 2.31 (1H, dd, J=14.2, 3.7 Hz, H-11), 2.10–2.05 (2H, m, H-2), 2.04–1.98 (1H, m, H-7), 1.82 (1H, ddd,

J=12.8, 6.5, 6.5 Hz, H-3), 1.65–1.62 (1H, m, H-8), 1.51 (1H, ddd, J=12.8, 6.5, 6.5 Hz, H-3), 1.50–1.38 (2H, m, H-6), 1.42–1.30 (1H, m, H-11), 1.40–1.30 (1H, m, H-7), 1.27 and 1.25 (3H, s each, Me-14, Me-16), 1.13 (3H, s, Me-19), 0.96 (3H, s, Me-20), 0.82 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 120.1 (C-1), 22.8 (C-2), 30.5 (C-3), 44.9 (C-4), 38.2 (C-5), 23.0 (C-6), 28.5 (C-7), 38.9 (C-8), 42.1 (C-9), 141.1 (C-10), 37.4 (C-11), 61.9 (C-12), 58.3 (C-13), 19.1 (C-14), 24.8 (C-16), 15.1 (C-17), 178.3 (C-18), 19.9 (C-19), 22.9 (C-20), 51.7 (–COO*Me*); EIMS: 320 (M^+), 302 (10), 234 (48), 175 (100), 105 (30), 85 (35); EIHRMS: calcd for $C_{20}H_{32}O_3$ $(M)^+$ 320.2351, found $(M)^+$ 320.2355.

3.5. Reaction of 11/12 with H_5IO_6: 13

A solution of H_5IO_6 (1.1 g, 4.77 mmol) in THF and H_2O (10 mL/9 mL) was added dropwise to a solution of **11/12** (694 mg, 2.17 mmol) in THF (10 mL). After stirring for 1 h, a 10% aqueous solution of Na_2SO_3 (200 mL) was added and the mixture was stirred for an additional 30 min. Extraction with EtOAc followed by successive washes with 10% Na_2SO_3, 6% $NaHCO_3$ and water. The organic layer was dried with Na_2SO_4 and evaporated in vacuo to obtain a residue, which was chromatographed over silica gel to yield **13** (483 mg, 80%).

3.5.1. Methyl 12-oxo-13,14,15,16-tetranor-*ent*-halim-1(10)-en-18-oate (13). $[\alpha]_D^{22}$ +9.6 (c 0.7, $CHCl_3$); mp: 60 °C; IR (film): 1723, 1462, 1383, 1244, 1167, 1117, 667 cm^{-1}; ^{1}H NMR δ: 9.57 (1H, dd, J=4.6, 1.8 Hz, H-12), 5.48 (1H, t, J=3.7 Hz, H-1), 3.63 (3H, s, –COOMe), 3.03 (1H, dd, J=14.6, 1.8 Hz, H-11), 2.87–2.81 (1H, m, H-5), 2.16–1.93 (4H, m), 1.80 (1H, ddd, J=12.4, 5.8, 5.8 Hz, H-3), 1.67–1.10 (5H, m), 1.13 (3H, s, Me-19), 1.06 (3H, s, Me-20), 0.82 (3H, d, J=6.8 Hz, Me-17); ^{13}C NMR δ: 121.2 (C-1), 23.2 (C-2), 30.0 (C-3), 45.1 (C-4), 38.7 (C-5), 23.4 (C-6), 28.9 (C-7), 39.3 (C-8), 42.4 (C-9), 140.3 (C-10), 51.7 (C-11), 205.1 (C-12), 14.9 (C-17), 178.3 (C-18), 21.1 (C-19), 23.7 (C-20), 52.0 (–COO*Me*); EIMS: 278 (M^+), 260 (5), 234 (90), 201 (55), 175 (100), 145 (20), 105 (40), 77 (15); EIHRMS: calcd for $C_{17}H_{26}O_3$ $(M)^+$ 278.1882, found $(M)^+$ 278.1881.

3.6. Reaction of 2 with UHP/TFAA: 7

An ice cooled solution of **2** (1.41 g, 4.59 mmol), UHP (5.49 mg, 58.35 mmol) in CH_2Cl_2 (55 mL) was treated with TFAA (4.6 mL, 32.57 mmol) under argon. The reaction mixture was stirred at room temperature for 1 h, then a 40% aqueous solution of $NaHSO_3$ was added and stirred for additional 30 min. The mixture was extracted with Et_2O, washed with a 6% aqueous solution of $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4), evaporated and chromatographed on silica gel (hexane/EtOAc 95:5) to obtain **7** (1.43 mg, 95%).

3.6.1. Methyl 12-acetoxy-1β,10β-epoxy-13,14,15,16-tetranor-*ent*-haliman-18-oate (7). $[\alpha]_D^{22}$ +52.1 (c 0.4, $CHCl_3$); mp: 55 °C; IR (film): 1736, 1464, 1373, 1246, 1125, 1030 cm^{-1}; ^{1}H NMR δ: 4.21 and 4.08 (1H, dt each, J_{AB}=11.4, 5.7 Hz, H-12), 3.62 (3H, s, –COO*Me*), 2.96 (1H, s, H-1), 2.78–2.72 (1H, m, H-5), 2.40–2.30 (1H, m), 2.22–2.00 (2H, m), 2.03 (3H, s, *Me*COO–), 1.82–1.73 (1H, m), 1.71–1.55 (3H, m), 1.45–1.38 (2H, m), 1.23–1.12 (2H, m), 0.95 (3H, s, Me-19), 0.91 (3H, d, J=6.8 Hz, Me-17), 0.72 (3H, s, Me-20); ^{13}C NMR δ: 53.6 (C-1), 20.1 (C-2), 23.2 (C-3), 42.4 (C-4), 38.6 (C-5), 21.0 (C-6), 28.3 (C-7), 38.7 (C-8), 39.3 (C-9), 64.4 (C-10), 36.5 (C-11), 61.6 (C-12), 14.9 (C-17), 177.4 (C-18), 25.4 (C-19), 15.5 (C-20), 51.3 (–COO*Me*), 21.1 (*Me*COO–), 170.4 (Me*C*OO–); EIMS: 279 (M^+−59, 12), 263 (10), 219 (21), 203 (14), 192 (51), 173 (61), 163 (38), 119 (38), 105 (63), 91 (58), 55 (100); EIHRMS: calcd for $C_{19}H_{30}O_5$ $(M)^+$ 338.2093, found $(M)^+$ 338.2097.

3.7. Reaction of 7 with $BF_3{\cdot}Et_2O$: 8

A solution of **7** (403 mg, 1.19 mmol) in dry C_6H_6 (13 mL) under argon was treated with $BF_3{\cdot}Et_2O$ (0.33 mL), and the reaction mixture was stirred at room temperature for 2 h. Following the same procedure described above, a residue was obtained and purified by chromatography on silica gel *n*-hexane/EtOAc (9:1) to afford **8** (174 mg, 43%).

3.7.1. Methyl 12-acetoxy-1β-hydroxy-13,14,15,16-tetranor-*ent*-labd-8-en-18-oate (8). $[\alpha]_D^{22}$ −51.2 (c 0.8, $CHCl_3$); IR (film): 3438, 2932, 1732, 1468, 1375, 1238, 1118, 1041 cm^{-1}; ^{1}H NMR δ: 4.29 (1H, ddd, J=10.8, 8.7, 7.6 Hz, H_A-12), 4.09 (1H, ddd, J=10.8, 8.6, 7.4 Hz, H_B-12), 4.01 (1H, br s, H-1), 3.67 (3H, s, –COO*Me*), 2.40–1.05 (11H, m), 2.05 (3H, s, *Me*COO–), 1.66 (3H, s, Me-17), 1.21 (3H, s, Me-19), 1.01 (3H, s, Me-20); ^{13}C NMR δ: 70.5 (C-1), 26.5 (C-2), 29.5 (C-3), 43.6 (C-4), 39.2 (C-5), 21.1 (C-6), 33.2 (C-7), 132.3 (C-8), 133.1 (C-9), 47.4 (C-10), 24.9 (C-11), 63.9 (C-12), 20.9 (C-17), 178.9 (C-18), 20.3 (C-19), 16.4 (C-20), 51.9 (–COO*Me*), 21.0 (*Me*COO–), 171.1 (Me*C*OO–); EIMS: 278 (M^+−60, 8), 207 (15), 149 (100), 121 (9), 91 (14), 73 (44); EIHRMS: calcd for $C_{19}H_{30}O_5$ (M^++Na) 361.1985, found (M^++Na) 361.1994.

3.8. Reaction of 13 with $NaBH_4$: 14

To an ice cooled solution of **13** (483 mg, 1.74 mmol) in MeOH (17 mL), $NaBH_4$ (132 mg, 3.47 mmol) was added. After being stirred at room temperature for 15 min, the reaction mixture was diluted with Et_2O and water, acidified with a few drops of a 2 M aqueous solution of HCl, and extracted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel to afford **14** (443 mg, 91%).

3.8.1. Methyl 12-hydroxy-13,14,15,16-tetranor-*ent*-halim-1(10)-en-18-oate (14). $[\alpha]_D^{22}$ +68.9 (c 1.3, $CHCl_3$); IR (film): 3600 (br), 1726, 1713, 1462, 1381, 1242, 1167, 1117, 1049, 1022, 665 cm^{-1}; ^{1}H NMR δ: 5.34 (1H, t, J=3.4 Hz, H-1), 3.65 (3H, s, –COOMe), 3.56 (2H, t, J=7.2 Hz, H-12), 2.76 (1H, dd, J=12.4, 2.4 Hz, H-5), 2.31 (1H, ddd, J=12.6, 7.0, 7.0 Hz, H-3), 2.10–1.98 (3H, m), 1.75 (1H, ddd, J=12.6, 5.8, 5.8 Hz, H-3), 1.57–1.16 (6H, m), 1.11 (3H, s, Me-19), 0.92 (3H, s, Me-20), 0.78 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 120.1 (C-1), 23.3 (C-2), 30.0 (C-3), 45.2 (C-4), 38.5 (C-5), 23.6 (C-6), 28.8 (C-7), 39.6 (C-8), 42.5 (C-9), 141.6 (C-10), 42.0 (C-11), 59.9 (C-12), 15.4 (C-17), 179.0 (C-18), 21.3 (C-19), 22.8 (C-20), 52.1 (–COO*Me*); EIMS: 280 (M^+, 10), 235 (95), 203 (10), 175 (100), 147 (12), 105 (30), 79 (10);

EIHRMS: calcd for $C_{17}H_{28}O_3$ $(M)^+$ 280.2038, found $(M)^+$ 280.2040.

3.9. Reaction of 14 with TBDMSCl: 15

To an ice cooled solution of **14** (439 mg, 1.57 mmol) in DMF (16 mL) TBDMSCl (282 mg, 1.88 mmol) and imidazol (215 mg, 3.13 mmol) were added under argon, and the mixture was stirred at room temperature for 18 h. Upon cooling to 0 °C the reaction mixture was diluted with water, and then extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **15** (605 mg, 98%).

3.9.1. Methyl 12-*tert*-butyldimethylsilyloxy-13,14,15,16-tetranor-*ent*-halim-1(10)-en-18-oate (15). $[\alpha]_D^{22}$ +14.2 (*c* 0.9, $CHCl_3$); IR (film): 1732, 1462, 1381, 1250, 1165, 1088, 837, 777, 667 cm^{-1}; ^1H NMR δ: 5.35 (1H, br s, H-1), 3.65 (3H, s, –COOMe), 3.52 (2H, t, *J*=7.6 Hz, H-12), 2.80–2.60 (1H, m, H-5), 2.18–1.95 (3H, m), 1.85–1.70 (1H, m), 1.65–1.18 (7H, m), 1.11 (3H, s, Me-19), 0.96 (3H, s, Me-20), 0.89 (9H, s, Me_3C–), 0.78 (3H, d, *J*=7.0 Hz, Me-17), 0.05 (6H, s, Me_2Si–); ^{13}C NMR δ: 119.5 (C-1), 22.8 (C-2), 31.3 (C-3), 45.1 (C-4), 38.7 (C-5), 22.9 (C-6), 28.6 (C-7), 38.8 (C-8), 42.0 (C-9), 141.3 (C-10), 41.9 (C-11), 60.4 (C-12), 15.4 (C-17), 178.7 (C-18), 19.5 (C-19), 23.3 (C-20), 51.9 (–COO*Me*), 18.6 (Me_3C–), 26.3 (Me_3C–), −5.0 (Me_2Si–); EIMS: 394 (M^+, 1), 363 (5), 337 (100), 219 (10), 177 (20), 147 (5), 105 (15), 73 (20); EIHRMS: calcd for $C_{23}H_{42}O_3Si$ $(M)^+$ 394.2903, found $(M)^+$ 394.2895.

3.10. Reduction of 15 with $LiAlH_4$: 16

An ice cooled solution of aldehyde **15** (503 mg, 1.28 mmol) in dry Et_2O (13 mL) was treated with $LiAlH_4$ (48 mg, 1.28 mmol) and was stirred at room temperature for 30 min. Then cooled back to 0 °C and wet Et_2O was added, filtered and concentrated in vacuo. The residue was chromatographed over silica gel to give **16** (458 mg, 98%).

3.10.1. 12-*tert*-Butyldimethylsilyloxy-13,14,15,16-tetranor-*ent*-halim-1(10)-en-18-ol (16). $[\alpha]_D^{22}$ +36.8 (*c* 1.3, $CHCl_3$); IR (film): 3400 (br), 1462, 1379, 1254, 1088, 835, 777, 665 cm^{-1}; ^1H NMR δ: 5.35 (1H, br s, H-1), 3.60–3.38 (2H, m, H-12), 3.42 (1H, d, *J*=11.4 Hz, H-18), 3.31 (1H, d, *J*=11.4 Hz, H-18), 2.21–1.85 (4H, m), 1.60–1.10 (8H, m), 0.92 (3H, s, Me-20), 0.87 (9H, s, Me_3C–), 0.84 (3H, s, Me-19), 0.77 (3H, d, *J*=7.0 Hz, Me-17), 0.03 (6H, s, Me_2Si–); ^{13}C NMR δ: 120.0 (C-1), 22.7 (C-2), 29.2 (C-3), 36.7 (C-4), 38.0 (C-5), 23.4 (C-6), 28.8 (C-7), 39.2 (C-8), 42.2 (C-9), 141.4 (C-10), 41.7 (C-11), 60.6 (C-12), 15.3 (C-17), 69.8 (C-18), 20.7 (C-19), 23.2 (C-20), 18.5 (Me_3C–), 26.2 (Me_3C–), −4.9 (Me_2Si–); EIMS: 366 (M^+, 1), 336 (10), 309 (15), 177 (100), 95 (30), 75 (40); EIHRMS: calcd for $C_{22}H_{42}O_2Si$ $(M)^+$ 366.2954, found $(M)^+$ 366.2960.

3.11. Oxidation of 16 with TPAP: 17

To a mixture of **16** (341 mg, 0.93 mmol), *N*-methylmorpholine *N*-oxide (NMO) (189 mg, 1.40 mmol) and molecular sieves (466 mg, 500 mg/mmol) in dry CH_2Cl_2 (10 mL) under argon, at room temperature was added TPAP (16 mg, 0.05 mmol). The reaction mixture was stirred for 1 h and then was filtered through a short pad of silica gel eluting with EtOAc. The solvent was evaporated to yield **17** (310 mg, 91%).

3.11.1. 12-*tert*-Butyldimethylsilyloxy-13,14,15,16-tetranor-*ent*-halim-1(10)-en-18-al (17). $[\alpha]_D^{22}$ +36.0 (*c* 0.3, $CHCl_3$); IR (film): 1728, 1458, 1254, 1088, 837, 775, 665 cm^{-1}; ^1H NMR δ: 9.42 (1H, s, H-18), 5.35 (1H, t, *J*=3.4 Hz, H-1), 3.52 (2H, t, *J*=7.3 Hz, H-12), 2.55–2.40 (1H, m, H-5), 2.20–1.95 (3H, m), 1.68–1.05 (8H, m), 0.95 (3H, s, Me-20), 0.88 (3H, s, Me-19), 0.87 (9H, s, Me_3C–), 0.77 (3H, d, *J*=7.0 Hz, Me-17), 0.03 (6H, s, Me_2Si–); ^{13}C NMR δ: 120.1 (C-1), 22.3 (C-2), 28.7 (C-3), 48.1 (C-4), 36.2 (C-5), 23.1 (C-6), 27.9 (C-7), 38.9 (C-8), 42.2 (C-9), 141.0 (C-10), 41.8 (C-11), 60.4 (C-12), 15.3 (C-17), 206.3 (C-18), 17.2 (C-19), 23.2 (C-20), 18.5 (Me_3C–), 23.2 (Me_3C–), −5.0 (Me_2Si–); EIMS: 364 (M^+, 1), 307 (55), 215 (10), 189 (100), 161 (30), 105 (40), 75 (55); EIHRMS: calcd for $C_{22}H_{40}O_2Si$ $(M)^+$ 364.2797, found $(M)^+$ 364.2804.

3.12. Addition to aldehyde 17: 18

2-(2-Bromoethyl)-2,5,5-trimethyl-1,3-dioxane (1.1 mL, 5.45 mmol) in THF (10 mL) was added to magnesium turnings (135 mg, 5.56 mmol) under argon and the mixture heated at 35 °C for 30 min. The Grignard reagent was then cooled to 0 °C and a solution of aldehyde **17** (310 mg, 0.85 mmol) in THF (3 mL) was added. After being stirred for 45 min at room temperature, the reaction mixture was quenched by the addition of aqueous ammonium chloride and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and gave the alcohol **18** (413 mg, 93%).

3.12.1. 16-*tert*-Butyldimethylsilyloxy-4-[(2,2-dimethyl)-propylendioxy]-4,5-seco-8(18→14)-*abeo*-picras-7-en-1-ol (18). $[\alpha]_D^{22}$ +7.3 (*c* 1.4, $CHCl_3$); IR (film): 3478, 1462, 1379, 1252, 1090, 835, 777, 665 cm^{-1}; ^1H NMR δ: 5.35–5.30 (1H, m, H-7), 3.61–3.37 (7H, m, H-1, H-16, –$C(OCH_2)_2$–), 2.48–2.07 (1H, m), 2.05–1.83 (6H, m), 1.80–1.40 (7H, m), 1.37 (3H, s, Me-19), 1.35–1.05 (2H, m), 1.05 and 0.82 (3H, s each, Me_2C–), 0.93 (3H, s, Me-18), 0.85 (9H, s, Me_3C–), 0.80 (3H, s, Me-20), 0.77 (3H, d, *J*=7.0 Hz, Me-17), 0.01 (6H, s, Me_2Si–); ^{13}C NMR δ: 75.3 (C-1), 25.0 (C-2), 37.6 (C-3), 99.4 (C-4), 27.3 (C-5), 22.6 (C-6), 120.3 (C-7), 141.7 (C-8), 37.7 (C-9), 39.0 (C-10), 22.2 (C-11), 29.0 (C-12), 38.7 (C-13), 42.1 (C-14), 41.9 (C-15), 60.5 (C-16), 15.5 (C-17), 19.8 (C-18), 19.8 (C-19), 18.5 (C-20), 23.2/22.6 (Me_2C–), 30.1 (Me_2C–), 70.5 (–$C(OCH_2)_2$–), 18.6 (Me_3C–), 26.2 (Me_3C–), −4.9 (Me_2Si–); EIMS: 522 (M^+, 2), 299 (10), 260 (15), 177 (15), 129 (100), 69 (65); EIHRMS: calcd for $C_{31}H_{58}O_4Si$ $(M)^+$ 522.4104, found $(M)^+$ 522.4098.

3.13. Reaction of 18 with TBAF: 19 and 20

A solution of **18** (135 mg, 0.26 mmol) in THF (3.0 mL) was treated with TBAF (0.78 mL, 0.78 mmol). After being

stirred for 90 min under argon, the reaction mixture was diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography C_6H_6/EtOAc (6:4) to give **19** (59 mg, 56%) and **20** (23 mg, 22%).

3.13.1. 4-[(2,2-Dimethyl)-propylendioxy]-4,5-seco-8(18→14)-*abeo*-picras-7-en-1*S*,16-diol (19). $[\alpha]_D^{22}$ +34.8 (*c* 0.6, $CHCl_3$); IR (film): 3430, 1462, 1379, 1250, 1213, 1088, 1049, 731, 667 cm^{-1}; ^1H NMR δ: 5.35 (1H, t, *J*=3.3 Hz, H-7), 3.70–3.30 (7H, m, H-1, H-16, –C(OCH_2)$_2$–), 2.65–1.90 (7H, m), 1.80–1.20 (9H, m), 1.39 (3H, s, Me-19), 1.09 and 0.80 (3H, s each, Me_2C–), 0.91 (3H, s, Me-18), 0.78 (3H, d, *J*=6.6 Hz, Me-17), 0.76 (3H, s, Me-20); ^{13}C NMR δ: 74.6 (C-1), 24.9 (C-2), 38.8 (C-3), 99.4 (C-4), 27.0 (C-5), 23.9 (C-6), 120.4 (C-7), 141.9 (C-8), 38.1 (C-9), 38.8 (C-10), 22.7 (C-11), 29.4 (C-12), 39.9 (C-13), 42.3 (C-14), 42.0 (C-15), 59.7 (C-16), 15.4 (C-17), 22.5 (C-18), 19.1 (C-19), 18.6 (C-20), 23.1/22.6 (Me_2C–), 30.1 (Me_2C–), 70.6 (–C(OCH_2)$_2$–); EIMS: 408 (M^+, 3), 393 (5), 304 (20), 259 (35), 218 (20), 173 (50), 101 (100); EIHRMS: calcd for $C_{25}H_{44}O_4$ $(M)^+$ 408.3240, found $(M)^+$ 408.3143.

3.13.2. 4-[(2,2-Dimethyl)-propylendioxy]-4,5-seco-8(18→14)-*abeo*-picras-7-en-1*R*,16-diol (20). $[\alpha]_D^{22}$ +33.9 (*c* 0.4, $CHCl_3$); IR (film): 3430, 1460, 1379, 1250, 1250, 1086, 1049, 667 cm^{-1}; ^1H NMR δ: 5.35 (1H, br s, H-7), 4.22 (1H, dd, *J*=5.6, 1.0 Hz, H-1), 3.62–3.50 (6H, m, H-16, –C(OCH_2)$_2$–), 2.80–2.20 (4H, m), 2.15–1.90 (5H, m), 1.85–1.05 (7H, m), 1.38 (3H, s, Me-19), 1.05 and 0.85 (3H, s each, Me_2C–), 0.91 (3H, s, Me-18), 0.80 (3H, s, Me-20), 0.79 (3H, d, *J*=7.0 Hz, Me-17); ^{13}C NMR δ: 73.9 (C-1), 24.9 (C-2), 36.8 (C-3), 99.3 (C-4), 27.8 (C-5), 24.7 (C-6), 120.0 (C-7), 142.5 (C-8), 38.0 (C-9), 38.7 (C-10), 22.8 (C-11), 29.7 (C-12), 40.5 (C-13), 43.1 (C-14), 42.1 (C-15), 60.3 (C-16), 15.4 (C-17), 22.6 (C-18), 20.3 (C-19), 18.2 (C-20), 23.1/22.7 (Me_2C–), 30.1 (Me_2C–), 70.6 (–C(OCH_2)$_2$–); EIMS: 408 (M^+, 1), 279 (30), 218 (5), 167 (40), 149 (100), 112 (30), 57 (78); EIHRMS: calcd for $C_{25}H_{44}O_4$ $(M)^+$ 408.3240, found $(M)^+$ 408.3248.

3.14. Acetylation of 19: 21

To a solution of **19** (42 mg, 0.10 mmol) in dry pyridine (2 mL) acetic anhydride (1 mL) was added and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into ice water and extracted with Et_2O. The organic layer was washed successively with aqueous 2 M HCl, aqueous 6% $NaHCO_3$ and water. The resulting solution was then dried (Na_2SO_4) and evaporated to obtain **21** (41 mg, 81%).

3.14.1. Diacetate of 4-[(2,2-dimethyl)-propylendioxy]-4,5-seco-8(18→14)-*abeo*-picras-7-en-1*S*,16-diol (21). $[\alpha]_D^{22}$ −29.8 (*c* 1.8, $CHCl_3$); IR (film): 1738, 1373, 1240, 1088, 1026 cm^{-1}; ^1H NMR δ: 5.42 (1H, br s, H-7), 4.98 (1H, d, *J*=8.4 Hz, H-1), 3.97 (1H, ddd, *J*=10.6, 10.6, 4.4 Hz, H-16), 3.86 (1H, ddd, *J*=10.6, 10.6, 4.4 Hz, H-16), 3.48 (2H, d, *J*=13.9 Hz, –C(OCH_2)$_2$–), 3.38 (2H, d, *J*=13.9 Hz, –C(OCH_2)$_2$–), 2.20–1.85 (5H, m), 2.06 and 1.99 (3H, s each, MeCOO–), 1.70–1.10 (11H, m), 1.34 (3H, s, Me-19), 1.00 and 0.87 (3H, s each, Me_2C–), 0.96 (3H, s, Me-18), 0.82 (3H, s, Me-20), 0.79 (3H, d, *J*=7.0 Hz, Me-17); ^{13}C NMR δ: 77.6 (C-1), 23.2 (C-2), 35.5 (C-3), 98.9 (C-4), 28.1 (C-5), 22.3 (C-6), 121.0 (C-7), 140.5 (C-8), 37.7 (C-9), 39.1 (C-10), 21.6 (C-11), 28.6 (C-12), 38.6 (C-13), 42.0 (C-14), 37.4 (C-15), 62.3 (C-16), 15.5 (C-17), 23.4 (C-18), 20.7 (C-19), 18.6 (C-20), 21.3/21.2 (*Me*COO–), 171.4/171.2 (Me*C*OO–), 23.0/22.7 (Me_2C–), 30.1 (Me_2C–), 70.5 (–C(OCH_2)$_2$–); EIMS: 492 (M^+, 1), 477 (10), 241 (20), 173 (10), 129 (50), 84 (100); EIHRMS: calcd for $C_{29}H_{48}O_6$ $(M)^+$ 492.3451, found $(M)^+$ 492.3542.

3.15. Acetylation of 20: 22

To a solution of **20** (15 mg, 0.04 mmol) in dry pyridine (1.0 mL) acetic anhydride (0.5 mL) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into ice water and extracted with Et_2O. The organic layer was washed successively with aqueous 2 M HCl, aqueous 6% $NaHCO_3$ and water and dried (Na_2SO_4). Concentration of the extract followed by purification of the residue by chromatography on silica gel to give the diacetyl derivative **22** (15 mg, 83%).

3.15.1. Diacetate of 4-[(2,2-dimethyl)-propylendioxy]-4,5-seco-8(18→14)-*abeo*-picras-7-en-1*R*,16-diol (22). $[\alpha]_D^{22}$ +14.3 (*c* 0.9, $CHCl_3$); IR (film): 1738, 1370, 1238, 1070, 1020 cm^{-1}; ^1H NMR δ: 5.45 (1H, br s, H-7), 4.89 (1H, d, *J*=9.2 Hz, H-1), 4.07 (1H, ddd, *J*=10.6, 10.6, 6.4 Hz, H-16), 3.84 (1H, ddd, *J*=10.6, 10.6, 5.6 Hz, H-16), 3.60 (2H, d, J_{AB}=11.4 Hz, –C(OCH_2)$_2$–), 3.40 (2H, dd, *J*=11.4, 3.2 Hz, –C(OCH_2)$_2$–), 2.15–1.80 (5H, m), 2.06 and 2.02 (3H, s each, MeCOO–), 1.75–1.10 (11H, m), 1.35 (3H, s, Me-19), 1.00 and 0.88 (3H, s each, Me_2C–), 0.97 (3H, s, Me-18), 0.82 (3H, s, Me-20), 0.80 (3H, d, *J*=7.0 Hz, Me-17); ^{13}C NMR δ: 78.7 (C-1), 23.4 (C-2), 35.3 (C-3), 98.9 (C-4), 28.7 (C-5), 22.7 (C-6), 121.2 (C-7), 140.8 (C-8), 38.1 (C-9), 39.1 (C-10), 22.4 (C-11), 28.8 (C-12), 38.5 (C-13), 42.1 (C-14), 37.3 (C-15), 62.3 (C-16), 15.5 (C-17), 23.2 (C-18), 20.8 (C-19), 18.3 (C-20), 21.4/21.3 (*Me*COO–), 171.3/171.2 (Me*C*OO–), 23.0/22.7 (Me_2C–), 30.1 (Me_2C–), 70.5 (–C(OCH_2)$_2$–); EIMS: 492 (M^+, 1), 477 (15), 432 (10), 328 (10), 241 (20), 203 (10), 129 (100), 69 (60); EIHRMS: calcd for $C_{29}H_{48}O_6$ $(M)^+$ 492.3451, found $(M)^+$ 492.3446.

3.16. Deprotection of 21 with *p*-TsOH: 23

To a solution of **21** (32 mg, 0.07 mmol) in acetone (distilled over $KMnO_4$, 1 mL) was added *p*-TsOH (1.2 mg, 0.007 mmol). The reaction mixture was stirred for 35 min, diluted with H_2O, and extracted with EtOAc. The organic phase was washed with an aqueous solution of $NaHCO_3$ (6%), H_2O, brine and dried over Na_2SO_4. The solvent was evaporated to afford **23** (26 mg, 98%).

3.16.1. 1*S*,16-Diacetoxy-4,5-seco-8(18→14)-*abeo*-picras-7-en-4-one (23). $[\alpha]_D^{22}$ −17.7 (*c* 1.3, $CHCl_3$); IR (film): 1732, 1464, 1437, 1371, 1240, 1032, 986 cm^{-1}; ^1H NMR δ: 5.40 (1H, t, *J*=2.6 Hz, H-7), 4.93 (1H, dd, *J*=10.9, 1.6 Hz, H-1), 3.96 (1H, ddd, *J*=10.6, 10.6, 6.0 Hz, H-16), 3.82 (1H, ddd, *J*=10.6, 10.6, 5.0 Hz, H-16), 2.47 (1H, ddd,

J=18.0, 9.2, 5.9 Hz, H-3), 2.36 (1H, ddd, J=18.0, 9.2, 5.0 Hz, H-3), 2.18 (1H, ddd, J=13.6, 10.6, 5.0 Hz, H-15), 2.11 (3H, s, Me-19), 2.03 (3H, s, *Me*COOC-1), 2.01–1.90 (1H, m, H-9), 2.00–1.90 (2H, m, H-6), 1.98 (3H, s, *Me*COOC-16), 1.96–1.86 (1H, m, H-12), 1.75–1.65 (2H, m, H-2), 1.65–1.55 (2H, m, H-11), 1.61–1.46 (1H, m, H-13), 1.49 (1H, ddd, J=13.6, 10.6, 6.0 Hz, H-15), 1.45–1.32 (2H, m, H-5), 1.38–1.28 (1H, m, H-12), 0.95 (3H, s, Me-18), 0.84 (3H, s, Me-20), 0.79 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 76.2 (C-1), 23.3 (C-2), 40.7 (C-3), 208.2 (C-4), 27.5 (C-5), 22.1 (C-6), 120.9 (C-7), 139.9 (C-8), 37.6 (C-9), 38.7 (C-10), 22.0 (C-11), 28.5 (C-12), 38.6 (C-13), 41.8 (C-14), 37.0 (C-15), 62.0 (C-16), 15.1 (C-17), 22.9 (C-18), 29.9 (C-19), 18.4 (C-20), 20.8 (*Me*COOC-1), 171.2 (Me*C*OOC-1), 20.9 (*Me*COOC-16), 170.9 (Me*C*OOC-16); EIMS: 406 (M^+), 346 (15), 337 (25), 259 (75), 231 (40), 201 (80), 173 (95), 145 (50), 105 (60), 85 (60); EIHRMS: calcd for $C_{24}H_{38}O_5$ $(M)^+$ 406.2719, found $(M)^+$ 406.2723.

3.17. Deprotection of 22 with *p*-TsOH: 24

To a solution of **22** (9 mg, 0.02 mmol) in acetone (distilled over $KMnO_4$, 0.5 mL) was added *p*-TsOH (0.3 mg, 0.002 mmol). The reaction mixture was stirred for 45 min, diluted with H_2O, and extracted with EtOAc. The organic phase was washed with an aqueous solution of $NaHCO_3$ (6%), H_2O, brine and dried over Na_2SO_4. The solvent was evaporated to afford **24** (7 mg, 94%).

3.17.1. 1*R*,16-Diacetoxy-4,5-seco-8(18→14)-*abeo*-picras-7-en-4-one (24). $[\alpha]_D^{22}$ +18.7 (*c* 0.6, $CHCl_3$); IR (film): 1732, 1460, 1437, 1360, 1230, 1030, 978 cm^{-1}; ^{1}H NMR δ: 5.45 (1H, br s, H-7), 4.96 (1H, dd, J=11.0, 1.8 Hz, H-1), 4.05 (1H, ddd, J=10.8, 10.8, 6.4 Hz, H-16), 3.85 (1H, ddd, J=10.8, 10.8, 5.3 Hz, H-16), 2.55–2.25 (3H, m), 2.12 (3H, s, Me-19), 2.10–1.85 (4H, m), 2.06 and 2.03 (3H, s each, MeCOO–), 1.80–1.25 (9H, m), 0.96 (3H, s, Me-18), 0.82 (3H, s, Me-20), 0.79 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 77.9 (C-1), 23.5 (C-2), 40.6 (C-3), 208.5 (C-4), 28.4 (C-5), 22.5 (C-6), 121.2 (C-7), 140.7 (C-8), 38.1 (C-9), 39.0 (C-10), 22.3 (C-11), 28.6 (C-12), 38.5 (C-13), 42.1 (C-14), 37.4 (C-15), 62.3 (C-16), 15.5 (C-17), 23.1 (C-18), 30.3 (C-19), 18.3 (C-20), 21.4/21.3 (*Me*COO–), 171.5/171.4 (Me*C*OO–); EIMS: 406 (M^+, 1), 346 (15), 259 (50), 173 (55), 105 (50); EIHRMS: calcd for $C_{24}H_{38}O_5$ $(M)^+$ 406.2719, found $(M)^+$ 406.2712.

3.18. Reaction of 23 with Na_2CrO_4: 25

Na_2CrO_4 (1.5 g, 9.46 mmol), acetic anhydride (12 mL), acetic acid (7 mL) and NaOAc (1.0 g) were added to a solution of ketone **23** (744 mg, 1.83 mmol) in benzene (100 mL) and stirred at 60 °C for 22 h. The reaction mixture was cooled down to room temperature. Then, ice was added and the mixture extracted with EtOAc and washed with a 6% aqueous solution of $NaHCO_3$ water and brine. The organic layer was dried over Na_2SO_4 and evaporated to give a crude oil, which was chromatographed on silica gel to afford the expected compound **25** (513 mg, 67%).

3.18.1. 1*S*,16-Diacetoxy-4,5-seco-8(18→14)-*abeo*-picras-7-en-4,6-dione (25). $[\alpha]_D^{22}$ −20.1 (*c* 0.7, $CHCl_3$); IR (film): 1738, 1674, 1462, 1427, 1370, 1240, 1034, 974 cm^{-1}; ^{1}H NMR δ: 5.89 (1H, s, H-7), 4.95 (1H, d, J=11.0 Hz, H-1), 3.91–3.84 (2H, m, H-16), 2.51–1.49 (1H, m, H-9), 2.43–2.33 (2H, m, H-3), 2.37 (1H, d, J=15.6 Hz, H-5), 2.20 (1H, d, J=15.6 Hz, H-5), 2.18–2.09 (1H, m, H-15), 2.08 (3H, s, *Me*COOC-1), 2.07 (3H, s, Me-19), 1.95 (3H, s, *Me*COOC-16), 1.94–1.82 (2H, m, H-2), 1.85–1.73 (2H, m, H-11), 1.79–1.67 (1H, m, H-13), 1.63–1.51 (1H, m, H-15), 1.44–1.34 (2H, m, H-12), 1.09 (3H, s, Me-18), 0.94 (3H, s, Me-20), 0.79 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 74.9 (C-1), 23.2 (C-2), 39.9 (C-3), 207.5 (C-4), 43.8 (C-5), 198.3 (C-6), 124.9 (C-7), 167.0 (C-8), 39.3 (C-9), 41.9 (C-10), 21.2 (C-11), 27.5 (C-12), 38.8 (C-13), 43.5 (C-14), 37.7 (C-15), 61.1 (C-16), 15.3 (C-17), 22.4 (C-18), 29.9 (C-19), 18.4 (C-20), 20.7 (*Me*COOC-1), 170.8 (Me*C*OOC-1), 20.8 (*Me*COOC-16), 170.7 (Me*C*OOC-16); EIMS: 420 (M^+, 10), 360 (8), 276 (30), 217 (95), 153 (30), 107 (60), 77 (100); EIHRMS: calcd for $C_{24}H_{36}O_6$ $(M)^+$ 420.2512, found $(M)^+$ 420.2519.

3.19. Reaction of 24 with Na_2CrO_4: 26

Na_2CrO_4 (998 mg, 6.16 mmol), acetic anhydride (8 mL), acetic acid (4 mL) and NaOAc (656 mg) were added to a solution of ketone **24** (500 mg, 1.23 mmol) in benzene (60 mL) and stirred at 60 °C for 24 h. The reaction mixture was cooled down to room temperature. Then, ice was added and the mixture extracted with EtOAc and washed with a 6% aqueous solution of $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4 and evaporated to give a crude oil, which was chromatographed on silica gel to afford the expected compound **26** (269 mg, 52%).

3.19.1. 1*R*,16-Diacetoxy-4,5-seco-8(18→14)-*abeo*-picras-7-en-4,6-dione (26). $[\alpha]_D^{22}$ +7.3 (*c* 1.0, $CHCl_3$); IR (film): 1736, 1673, 1368, 1237, 1031 cm^{-1}; ^{1}H NMR δ: 5.89 (1H, s, H-7), 4.91 (1H, dd, J=10.9, 1.9 Hz, H-1), 3.98 (1H, ddd, J=10.0, 10.0, 4.0 Hz, H-16), 3.92 (1H, ddd, J=10.0, 10.0, 3.6 Hz, H-16), 2.65 (1H, dd, J=8.5, 6.9 Hz, H-9), 2.38–2.32 (2H, m, H-3), 2.29 (1H, d, J=8.2 Hz, H-5), 2.27 (1H, d, J=8.2 Hz, H-5), 2.13–2.07 (1H, m, H-15), 2.08 (3H, s, Me-19), 2.03–1.96 (2H, m, H-2), 1.99 (3H, s, *Me*COOC-1), 1.97 (3H, s, *Me*COOC-16), 1.88–1.82 (1H, m, H-15), 1.82–1.71 (1H, m, H-13), 1.80–1.71 (2H, m, H-11), 1.50–1.35 (2H, m, H-12), 1.04 (3H, s, Me-18), 0.90 (3H, s, Me-20), 0.80 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 77.1 (C-1), 23.4 (C-2), 39.7 (C-3), 207.6 (C-4), 44.3 (C-5), 198.4 (C-6), 124.9 (C-7), 167.4 (C-8), 39.0 (C-9), 42.0 (C-10), 22.1 (C-11), 27.5 (C-12), 38.6 (C-13), 43.5 (C-14), 37.7 (C-15), 61.1 (C-16), 15.4 (C-17), 22.3 (C-18), 29.9 (C-19), 19.3 (C-20), 20.7 (*Me*COOC-1), 170.9 (Me*C*OOC-1), 20.9 (*Me*COOC-16), 170.8 (Me*C*OOC-16); EIMS: 420 (M^+, 10), 360 (5), 276 (25), 217 (100), 161 (25), 121 (35); EIHRMS: calcd for $C_{24}H_{36}O_6$ $(M)^+$ 420.2512, found $(M)^+$ 420.2518.

3.20. Reaction of 25 with KHMDS: 27–29

To a solution of KHMDS (0.5 M, toluene, 3.1 mL, 1.56 mmol) in THF (1 mL) cooled to −78 °C under an argon atmosphere was added a precooled solution of **25** (82 mg, 0.19 mmol) in THF (1 mL) via cannula. After 45 min at −78 °C, the reaction mixture was diluted with aqueous

solution of $NaHCO_3$ (6%), extracted with EtOAc and washed with water. The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (CH_3Cl/MeOH 99:1) to yield **27** (15 mg, 18%), **28** (41 mg, 50%) and **29** (13 mg, 16%).

The procedure was exactly as described above except that −100 °C was used as temperature of reaction to obtain **27** (12%), **28** (35%) and **29** (31%).

3.20.1. Compound 27. $[\alpha]_D^{22}$ +55.7 (*c* 0.4, $CHCl_3$); IR (film): 3461, 1738, 1713, 1462, 1377, 1242, 1034 cm^{-1}; ^1H NMR δ: 5.41 (1H, s, H-7), 4.62 (1H, dd, *J*=11.8, 5.7 Hz, H-1), 4.12 (1H, ddd, *J*=10.5, 10.5, 5.8 Hz, H-16), 4.01 (1H, ddd, *J*=10.5, 10.5, 5.8 Hz, H-16), 2.68 (1H, dd, *J*=13.0, 3.4 Hz, H-3), 2.46–2.35 (1H, m, H-9), 2.30–2.16 (1H, m, H-15), 2.20–2.05 (2H, m, H-12), 2.14 (3H, s, Me-19), 2.10 (3H, s, *Me*COOC-1), 2.03 (3H, s, *Me*COO, C-16), 1.83–1.75 (1H, m, H-15), 1.75 (1H, d, *J*=12.5 Hz, H-5), 1.70–1.65 (1H, m, H-13), 1.61–1.49 (1H, m, H-2), 1.47–1.33 (1H, m, H-2), 1.45–1.30 (2H, m, H-11), 1.34 (1H, d, *J*=12.5 Hz, H-5), 0.99 (3H, s, Me-18), 0.90 (3H, s, Me-20), 0.83 (3H, d, *J*=6.8 Hz, Me-17); ^{13}C NMR δ: 79.7 (C-1), 29.1 (C-2), 57.7 (C-3), 211.0 (C-4), 42.7 (C-5), 71.9 (C-6), 126.1 (C-7), 145.7 (C-8), 35.9 (C-9), 38.7 (C-10), 25.0 (C-11), 28.8 (C-12), 38.6 (C-13), 42.4 (C-14), 37.5 (C-15), 61.9 (C-16), 15.0 (C-17), 22.6 (C-18), 29.9 (C-19), 25.1 (C-20), 21.1 (*Me*COOC-1), 170.7 (Me*C*OOC-1), 21.0 (*Me*COOC-16), 170.8 (Me*C*OOC-16); EIMS: 420 (M^+, 5), 402 (10), 342 (10), 277 (15), 217 (90), 161 (40); EIHRMS: calcd for $C_{24}H_{36}O_6$ $(M)^+$ 420.2512, found $(M)^+$ 420.2518.

3.20.2. 1α,16-Diacetoxy-4β-hydroxy-8(18→14)-*abeo*-5-*epi*-picras-7-en-6-one (28). $[\alpha]_D^{22}$ −105.6 (*c* 0.5, $CHCl_3$); IR (film): 3493, 1738, 1651, 1462, 1368, 1236, 1036 cm^{-1}; ^1H NMR δ: 6.12 (1H, d, *J*=1.7 Hz, H-7), 4.69 (1H, dd, *J*=10.5, 2.8 Hz, H-1), 4.15 (1H, ddd, *J*=10.9, 10.8, 6.2 Hz, H-16), 4.03 (1H, ddd, *J*=10.9, 10.8, 5.6 Hz, H-16), 3.17 (1H, br s, –OH), 3.02 (1H, ddd, *J*=12.0, 5.8, 1.7 Hz, H-9), 2.32–2.15 (1H, m, H-11), 2.31–2.16 (1H, m, H-15), 2.24 (1H, s, H-5), 2.15–1.97 (1H, m, H-12), 2.07 (3H, s, *Me*COOC-1), 2.02 (3H, s, *Me*COOC-16), 1.95–1.78 (1H, m, H-13), 1.92–1.67 (2H, m, H-3), 1.87–1.72 (2H, m, H-2), 1.66–1.50 (1H, m, H-15), 1.65–1.51 (1H, m, H-11), 1.50–1.33 (1H, m, H-12), 1.14 (3H, s, Me-18), 1.07 (3H, s, Me-19), 1.02 (3H, s, Me-20), 0.85 (3H, d, *J*=7.0 Hz, Me-17); ^{13}C NMR δ: 80.4 (C-1), 24.9 (C-2), 38.9 (C-3), 71.1 (C-4), 64.7 (C-5), 200.1 (C-6), 125.7 (C-7), 171.2 (C-8), 36.8 (C-9), 41.0 (C-10), 22.7 (C-11), 27.4 (C-12), 35.4 (C-13), 43.9 (C-14), 38.3 (C-15), 60.7 (C-16), 15.7 (C-17), 23.7 (C-18), 25.5 (C-19), 23.1 (C-20), 21.3 (*Me*COOC-1), 169.9 (Me*C*OOC-1), 20.9 (*Me*COOC-16), 170.9 (Me*C*OOC-16); EIMS: 420 (M^+, 5), 277 (30), 217 (100), 121 (35); EIHRMS: calcd for $C_{24}H_{36}O_6$ $(M)^+$ 420.2512, found $(M)^+$ 420.2503.

3.20.3. Compound 29. $[\alpha]_D^{22}$ −0.5 (*c* 0.8, $CHCl_3$); IR (film): 3457, 1732, 1669, 1462, 1368, 1238, 1032, 735, 665 cm^{-1}; ^1H NMR δ: 5.97 (1H, d, *J*=1.7 Hz, H-7), 4.17 (1H, d, *J*=8.5 Hz, H-1), 4.10 (1H, ddd, *J*=17.0, 8.8, 6.4 Hz, H-16), 3.85 (1H, ddd, *J*=17.0, 8.8, 5.6 Hz, H-16), 2.97 (1H, d, *J*=13.7 Hz, C-21), 2.93 (1H, ddd, *J*=12.4, 6.0, 1.7 Hz, H-9), 2.74 (1H, dd, *J*=13.7, 2.0 Hz, C-21), 2.66 (1H, d, *J*=13.2 Hz, H-5), 2.21 (1H, d, *J*=13.2 Hz, H-5), 2.10–2.06 (1H, m, H-13), 2.09–1.98 (1H, m, H-12), 2.07–2.01 (1H, m, H-15), 2.04 (3H, s, MeCOO–), 2.03–1.96 (1H, m, H-3), 1.98–1.74 (2H, m, H-2), 1.97–1.60 (1H, m, H-15), 1.81–1.70 (2H, m, H-11), 1.67–1.52 (1H, m, H-3), 1.51–1.40 (1H, m, H-12), 1.37 (3H, s, Me-19), 1.11 (3H, s, Me-18), 0.99 (3H, s, Me-20), 0.86 (3H, d, *J*=7.2 Hz, Me-17); ^{13}C NMR δ: 82.1 (C-1), 38.2 (C-2), 41.5 (C-3), 68.5 (C-4), 43.4 (C-5), 198.2 (C-6), 125.0 (C-7), 167.7 (C-8), 38.3 (C-9), 42.5 (C-10), 24.5 (C-11), 27.1 (C-12), 37.9 (C-13), 43.5 (C-14), 20.5 (C-15), 67.0 (C-16), 15.5 (C-17), 22.7 (C-18), 32.5 (C-19), 18.1 (C-20), 47.1 (C-21), 170.9 (C-22), 20.9 (*Me*COO–), 171.0 (Me*C*OO); EIMS: 421 (M^++1, 10), 307 (15), 217 (10), 154 (95); EIHRMS: calcd for $C_{24}H_{37}O_6$ $(M+H)^+$ 421.2590, found $(M+H)^+$ 421.2597.

3.21. Reaction of 25 with LDA: 28

To a solution of *i*-Pr_2NH (0.17 mL, 1.04 mmol) in THF (1 mL) cooled to −78 °C under an argon atmosphere was added *n*BuLi (1.6 M in hexane, 0.59 mL, 0.94 mmol). The solution was stirred for 10 min and then a precooled solution of **25** (20 mg, 0.05 mmol) in THF (0.5 mL) was added via cannula. The mixture was stirred at −78 °C for 20 min. After that time, the resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was washed with aqueous solution of HCl (2 M), H_2O and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography (CH_3Cl) to yield **28** (6 mg, 30%).

3.21.1. Reaction of 25 with K_2CO_3/MeOH: 27 and 30. Compound **25** (22 mg, 0.05 mmol) was treated with K_2CO_3 in MeOH (1%, 0.5 mL) and the mixture was stirred at 0 °C for 15 min. After that time, the reaction mixture was diluted with H_2O and extracted with EtOAc. The organic phase was washed with aqueous solution of HCl (2 M), H_2O and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography (CH_3Cl/MeOH 50:0.2) to yield **27** (9 mg, 50%) and **30** (8 mg, 49%).

3.21.2. Compound 30. $[\alpha]_D^{22}$ +66.3 (*c* 0.9, $CHCl_3$); IR (film): 3405, 1738, 1711, 1451, 1377, 1242, 1034 cm^{-1}; ^1H NMR δ: 5.34 (1H, s, H-7), 4.60 (1H, dd, *J*=11.8, 5.6 Hz, H-1), 3.72–3.62 (2H, m, H-16), 2.74 (1H, dd, *J*=13.2, 4.2 Hz, H-3), 2.44 (1H, dd, *J*=12.2, 3.8 Hz, H-9), 2.30–1.95 (4H, m), 2.15 (3H, s, Me-19), 2.08 (3H, s, MeCOO–), 1.85–1.15 (7H, m), 0.98 (3H, s, Me-18), 0.88 (3H, s, Me-20), 0.81 (3H, d, *J*=6.6 Hz, Me-17); ^{13}C NMR δ: 80.1 (C-1), 29.2 (C-2), 57.9 (C-3), 211.1 (C-4), 43.4 (C-5), 72.2 (C-6), 125.7 (C-7), 146.8 (C-8), 36.1 (C-9), 39.1 (C-10), 25.3 (C-11), 29.1 (C-12), 39.1 (C-13), 42.6 (C-14), 42.2 (C-15), 60.2 (C-16), 15.3 (C-17), 23.2 (C-18), 30.9 (C-19), 25.3 (C-20), 21.5 (*Me*COO–), 170.9 (Me*C*OO–); EIMS: 378 (M^+, 2), 360 (20), 300 (20), 235 (25), 189 (20), 161 (20), 212 (100); EIHRMS: calcd for $C_{22}H_{34}O_5$ $(M)^+$ 378.2406, found $(M)^+$ 378.2410.

3.21.3. Reaction of 26 with KHMDS: 31 and 32. To a solution of KHMDS (0.5 M, toluene, 2.7 mL, 1.33 mmol) in THF (1 mL) cooled to −78 °C under an argon atmosphere

was added a precooled solution of **26** (80 mg, 0.19 mmol) in THF (1 mL) via cannula. The reaction mixture was stirred at −78 °C for 15 min. Following the same procedure described for **25**, the residue obtained was purified by flash chromatography (CH_3Cl) to yield **26** (7 mg, 9%), **31** (traces) and **32** (11 mg, 14%).

The procedure was exactly as described above except that −100 °C was used as temperature of reaction to obtain **26** (3 mg, 19%), **31** (traces) and **32** (4.2 mg, 26%).

3.21.4. 1β,16-Diacetoxy-4β-hydroxy-8(18→14)-*abeo*-5-*epi*-picras-7-en-6-one (32). $[\alpha]_D^{22}$ −47.2 (*c* 0.3, $CHCl_3$); IR (film): 3426, 1742, 1719, 1656, 1369, 1245, 1028 cm^{-1}; ^1H NMR δ: 6.12 (1H, s, H-7), 5.14 (1H, s, H-1), 4.15–3.93 (2H, m, H-16), 3.34 (1H, br s, –OH), 2.78–2.66 (1H, m, H-9), 2.53 (1H, s, H-5), 2.30–2.16 (1H, m, H-11), 2.10–1.95 (1H, m, H-12), 2.08 (3H, s, *Me*COOC-16), 2.01 (3H, s, *Me*COOC-1), 1.92–1.83 (1H, m, H-3), 1.90–1.82 (1H, m, H-13), 1.85–1.70 (2H, m, H-2), 1.67–1.58 (1H, m, H-15), 1.62–1.51 (1H, m, H-3), 1.60–1.50 (1H, m, H-11), 1.55–1.40 (1H, m, H-12), 1.47–1.36 (1H, m, H-15), 1.14 (3H, s, Me-18), 1.10 (3H, s, Me-19), 0.97 (3H, s, Me-20), 0.85 (3H, d, *J*=6.9 Hz, Me-17); ^{13}C NMR δ: 71.0 (C-1), 24.0 (C-2), 32.9 (C-3), 71.4 (C-4), 60.7 (C-5), 201.2 (C-6), 126.1 (C-7), 169.4 (C-8), 37.3 (C-9), 41.3 (C-10), 20.3 (C-11), 26.7 (C-12), 35.5 (C-13), 43.3 (C-14), 38.7 (C-15), 60.6 (C-16), 15.7 (C-17), 23.2 (C-18), 24.9 (C-19), 21.2 (C-20), 20.9 (*Me*COOC-1), 170.8 (Me*C*OOC-1), 21.0 (*Me*COOC-16), 170.3 (Me*C*OOC-16); EIMS: 420 (M^+, 1), 256 (20), 191 (10), 153 (35), 69 (100); EIHRMS: calcd for $C_{24}H_{36}O_6$ $(M)^+$ 420.2512, found $(M)^+$ 420.2519.

3.22. Reaction of 26 with LDA: 32

To a solution of *i*-Pr_2NH (0.93 mL, 5.70 mmol) in THF (5 mL) cooled to −78 °C under an argon atmosphere was added *n*-BuLi (1.6 M in hexane, 3.39 mL, 5.43 mmol). The solution was stirred for 10 min and then a precooled solution of **26** (114 mg, 0.27 mmol) in THF (2 mL) was added via cannula. The mixture was stirred at −78 °C for 20 min. After that time, the resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was washed with aqueous solution of HCl (2 M), H_2O and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography (CH_3Cl) to yield **32** (32 mg, 28%).

3.23. Reaction of 26 with LDE: 32

To a solution of Et_2NH (0.02 mL, 0.14 mmol) in THF (2 mL) cooled to −78 °C under an argon atmosphere was added *n*-BuLi (1.6 M in hexane, 0.1 mL, 0.14 mmol). The solution was stirred for 30 min and then a precooled solution of **26** (18 mg, 0.04 mmol) in THF (0.5 mL) was added via cannula. The mixture was stirred at −78 °C for 10 min. After the addition of saturated aqueous NH_4Cl, the resulting mixture was allowed to warm to room temperature and extracted with EtOAc. The organic phase was washed with H_2O, brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography (CH_3Cl) to yield **26** (3 mg, 9%) and **32** (5 mg, 15%).

3.24. Reaction of 28 with $SOCl_2$: 33 and 34

To an ice cooled solution of ketone **28** (5 mg, 0.01 mmol) in dry CH_2Cl_2 (13 mL) under argon $SOCl_2$ (0.002 mL, 0.03 mmol) and pyridine (0.1 mL) were added and the mixture was stirred at 0 °C for 30 min. After that time, the reaction mixture was extracted with EtOAc and washed with aqueous solution of $NaHCO_3$ (6%), aqueous solution of HCl (2 M) and H_2O. The organic layer was dried (Na_2SO_4) and evaporated to give **33** (3 mg, 54%) and **34** (2 mg, 36%).

3.24.1. 1α,16-Diacetoxy-8(18→14)-*abeo*-5-*epi*-picrasa-3,7-dien-6-one (33). $[\alpha]_D^{22}$ −105.2 (*c* 0.6, $CHCl_3$); IR (film): 1739, 1675, 1458, 1366, 1234, 1032 cm^{-1}; ^1H NMR δ: 5.85 (1H, d, *J*=1.8 Hz, H-7), 5.41 (1H, br s, H-3), 4.89 (1H, dd, *J*=9.4, 6.6 Hz, H-1), 3.83 (2H, t, *J*=8.1 Hz, H-16), 2.98–2.85 (1H, m, H-9), 2.73 (1H, br s, H-5), 2.60–1.85 (5H, m), 2.05 and 2.01 (3H, s each, MeCOO–), 1.80–1.20 (4H, m), 1.50 (3H, s, Me-19), 1.08 (3H, s, Me-18), 0.99 (3H, s, Me-20), 0.85 (3H, d, *J*=7.0 Hz, Me-17); ^{13}C NMR δ: 76.4 (C-1), 28.3 (C-2), 120.5 (C-3), 129.3 (C-4), 59.3 (C-5), 198.9 (C-6), 122.3 (C-7), 167.2 (C-8), 37.7 (C-9), 38.7 (C-10), 22.4 (C-11), 27.2 (C-12), 35.4 (C-13), 42.6 (C-14), 37.2 (C-15), 60.0 (C-16), 14.6 (C-17), 22.8 (C-18), 21.8 (C-19), 18.6 (C-20), 20.4/20.1 (*Me*COO–), 169.5/169.4 (Me*C*OO–); EIMS: 402 (M^+, 30), 314 (30), 227 (45), 194 (50), 161 (25), 105 (60), 69 (100); EIHRMS: calcd for $C_{24}H_{34}O_5$ $(M)^+$ 402.2406, found $(M)^+$ 402.2414.

3.24.2. 1α,16-Diacetoxy-8(18→14)-*abeo*-5-*epi*-picrasa-4(19),7-dien-6-one (34). $[\alpha]_D^{22}$ −23.7 (*c* 0.6, $CHCl_3$); IR (film): 1739, 1675, 1458, 1375, 1236, 1034 cm^{-1}; ^1H NMR δ: 6.01 (1H, s, H-7), 4.88 (1H, s, H-19), 4.76 (1H, dd, *J*=9.6, 4.0 Hz, H-1), 4.49 (1H, s, H-19), 3.96 (2H, t, *J*=7.3 Hz, H-16), 3.00–2.85 (1H, m), 2.75 (1H, br s, H-5), 2.58–2.10 (4H, m), 2.05–1.20 (7H, m), 2.03 and 2.02 (3H, s each, MeCOO–), 1.11 (3H, s, Me-18), 1.00 (3H, s, Me-20), 0.85 (3H, d, *J*=7.0 Hz, Me-17); EIMS: 402 (M^+, 30), 314 (20), 255 (50), 194 (25), 153 (55), 77 (100); EIHRMS: calcd for $C_{24}H_{34}O_5$ $(M)^+$ 402.2406, found $(M)^+$ 402.2411.

3.25. Reaction of 32 with $SOCl_2$: 35 and 36

To an ice cooled solution of ketone **32** (6 mg, 0.01 mmol) in dry CH_2Cl_2 (12 mL) under argon $SOCl_2$ (0.002 mL, 0.03 mmol) and pyridine (0.1 mL) were added and the mixture was stirred at 0 °C for 35 min. After that time, the reaction mixture was extracted with EtOAc and washed with aqueous solution of HCl (2 M), aqueous solution of $NaHCO_3$ (6%) and H_2O. The organic layer was dried (Na_2SO_4) and evaporated to give **35** (3 mg, 51%) and **36** (2 mg, 34%).

3.25.1. 1β,16-Diacetoxy-8(18→14)-*abeo*-5-*epi*-picrasa-3,7-dien-6-one (35). $[\alpha]_D^{22}$ −68.3 (*c* 0.4, $CHCl_3$); IR (film): 1742, 1666, 1463, 1375, 1238, 1036 cm^{-1}; ^1H NMR δ: 5.89 (1H, s, H-7), 5.41 (1H, br s, H-3), 5.08 (1H, br s, H-1), 3.95–3.73 (2H, m, H-16), 2.91 (1H, br s, H-5), 2.73–2.65 (1H, m, H-9), 2.70–2.62 (1H, m, H-15), 2.65–2.58 (1H, m, H-2), 2.15–2.08 (1H, m, H-2), 2.12–2.03 (1H, m, H-15), 2.10–2.01 (1H, m, H-12), 2.04 (3H, s, *Me*COOC-16), 2.02

(3H, s, *Me*COOC-1), 1.85–1.70 (1H, m, H-13), 1.64 (3H, s, Me-19), 1.53–1.40 (1H, m, H-12), 1.40–1.28 (2H, m, H-11), 1.09 (3H, s, Me-18), 0.99 (3H, s, Me-20), 0.86 (3H, d, J=7.0 Hz, Me-17), ^{13}C NMR δ: 71.0 (C-1), 29.2 (C-2), 119.2 (C-3), 130.0 (C-4), 54.5 (C-5), 201.2 (C-6), 123.9 (C-7), 166.8 (C-8), 37.0 (C-9), 39.7 (C-10), 21.2 (C-11), 27.6 (C-12), 38.4 (C-13), 43.2 (C-14), 37.8 (C-15), 60.9 (C-16), 15.4 (C-17), 22.6 (C-18), 22.5 (C-19), 18.5 (C-20), 21.1 (*Me*COOC-1), 170.7 (Me*C*OOC-1), 20.9 (*Me*COOC-16), 170.6 (Me*C*OOC-16); EIMS: 402 (M^+, 15), 314 (15), 273 (15), 227 (20), 194 (25); EIHRMS: calcd for $C_{24}H_{34}O_5$ $(M)^+$ 402.2406, found $(M)^+$ 402.2399.

3.25.2. 1β,16-Diacetoxy-8(18→14)-*abeo*-5-*epi*-picrasa-4(19),7-dien-6-one (36). IR (film): 1739, 1669, 1457, 1374, 1239, 1033, 667 cm^{-1}; ^{1}H NMR δ: 6.00 (1H, s, H-7), 5.02–4.95 (3H, m, H-1, H-19), 4.16–3.65 (2H, m, H-16), 2.98 (1H, br s, H-5), 2.70–2.50 (1H, m, H-9), 2.30–2.18 (2H, m), 2.06 and 2.02 (3H, s each, MeCOO–), 2.00–0.90 (9H, m), 1.09 (3H, s, Me-18), 1.01 (3H, s, Me-20), 0.83 (3H, d, J=7.0 Hz, Me-17); EIMS: 403 (M^++H, 100), 343 (50), 129 (20); EIHRMS: calcd for $C_{24}H_{35}O_5$ $(M+H)^+$ 403.2479, found $(M)^+$ 403.2478.

3.26. Reaction of 25 with LDA and $SOCl_2$: 33 and 34

To a solution of *i*-Pr_2NH (0.87 mL, 5.35 mmol) in THF (3 mL) cooled to −78 °C under an argon atmosphere was added *n*-BuLi (1.6 M in hexane, 3.18 mL, 5.09 mmol). The solution was stirred for 10 min and then a precooled solution of **25** (107 mg, 0.25 mmol) in THF (1 mL) was added via cannula. The mixture was stirred at −78 °C for 35 min. After that time, the resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was washed with aqueous solution of HCl (2 M), H_2O and dried over Na_2SO_4. After filtration, the solvent was evaporated to give ketone (90 mg), which was used in the next step without purification. To an ice cooled solution of ketone in dry CH_2Cl_2 (2 mL) under argon $SOCl_2$ (0.02 mL, 0.25 mmol) and pyridine (1 mL) were added and the mixture was stirred at 0 °C for 15 min. After that time, the reaction mixture was extracted with EtOAc and washed with aqueous solution of HCl (2 M), aqueous solution of $NaHCO_3$ (6%) and H_2O. The organic layer was dried (Na_2SO_4) and evaporated to give a residue, which was purified by flash chromatography (hexane/EtOAc 85:15→8:2) to yield **33** (13 mg, 13%) and **34** (14 mg, 14%).

3.27. Reaction of 26 with LDA and $SOCl_2$: 35 and 36

To a solution of *i*-Pr_2NH (0.45 mL, 2.75 mmol) in THF (2 mL) cooled to −78 °C under an argon atmosphere was added *n*-BuLi (1.6 M in hexane, 1.64 mL, 2.62 mmol). The solution was stirred for 10 min and then a precooled solution of **26** (55 mg, 0.13 mmol) in THF (1 mL) was added via cannula. The mixture was stirred at −78 °C for 35 min. After that time, the resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was washed with aqueous solution of HCl (2 M), H_2O and dried over Na_2SO_4. After filtration, the solvent was evaporated to give ketone (52 mg), which was used in the next step without purification. To an ice cooled solution of ketone in dry CH_2Cl_2 (1.2 mL) under argon $SOCl_2$ (0.01 mL, 0.17 mmol) and pyridine (0.6 mL) were added and the mixture was stirred at 0 °C for 35 min. After that time, the reaction mixture was extracted with EtOAc and washed with aqueous solution of HCl (2 M), aqueous solution of $NaHCO_3$ (6%) and H_2O. The organic layer was dried (Na_2SO_4) and evaporated to give a residue, which was purified by flash chromatography (hexane/EtOAc 8:2) to yield **35** (10 mg, 20%) and **36** (4 mg, 8%).

3.28. Reaction of 32 with *p*-TsOH: 26

To a solution of **32** (3 mg, 0.007 mmol) in benzene (0.16 mL) under argon was added *p*-TsOH (0.68 mg, 0.0003 mmol). The reaction mixture was heated at 45 °C with stirring for 75 min, allowed to cool to room temperature, diluted with H_2O and EtOAc and extracted with EtOAc. The organic phase was washed with aqueous solution of $NaHCO_3$ (6%), H_2O, and dried over Na_2SO_4. The solvent was evaporated to afford a residue, which was purified by flash chromatography (hexane/EtOAc 8:2) to yield **26** (1 mg, 33%).

3.29. Reduction of 32 with $LiALH_4$: 37

An ice cooled solution of ketone **32** (6 mg, 0.01 mmol) in dry Et_2O (0.5 mL) was treated with $LiAlH_4$ (2 mg, 0.06 mmol) and was stirred at room temperature for 4 h. Then, the reaction mixture was cooled back to 0 °C and the excess of $LiAlH_4$ was decomposed by dropwise addition of wet EtOAc. Evaporation of the dried solution gave tetraol **37** (4 mg, 83%).

3.30. 8(18→14)-*abeo*-5-*epi*-Picrasa-1β,4β,6,16-tetraol (37)

IR (film): 3354, 1463, 1379, 1260, 1089, 1024, 800 cm^{-1}; ^{1}H NMR δ: 5.55 (1H, s, H-7), 4.80–4.75 (1H, m, H-6), 3.80 (1H, br s, H-1), 3.65–3.55 (2H, m, H-16), 2.38–2.24 (2H, m, H-5 and H-9), 2.08–0.90 (11H, m), 1.34 (3H, s, Me-19), 1.06 (6H, s, Me-18, Me-20), 0.86 (3H, d, J=6.8 Hz, Me-17); EIMS: 320 (M^+−18, 1), 256 (15), 223 (10), 149 (30).

3.31. Reaction of 32 with ^{t}BuOOH/NaOH: 38

To a solution of **32** (9 mg, 0.02 mmol) in MeOH (1 mL) a solution of ^{t}BuOOH (6 M in decane 0.02 mL, 0.11 mmol) and NaOH (0.02 mL of a 2 M solution, 0.04 mmol) were added. The reaction mixture was heated at 45 °C with stirring for 6 h, allowed to cool to room temperature, diluted with H_2O and a few drop HCl and extracted with EtOAc. The organic phase was washed with H_2O and dried over Na_2SO_4. The solvent was evaporated to afford a residue, which was purified by flash chromatography (CH_3Cl/MeOH 9.85:0.15→9.75:0.25) to give **38** (2 mg, 28%).

3.31.1. Compound 38. $[\alpha]_D^{22}$ −27.7 (c 0.2, $CHCl_3$); IR (film): 3374, 1701, 1459, 1375, 1180, 1046 cm^{-1}; ^{1}H NMR δ: 3.70 (1H, t, J=2.5 Hz, H-1), 3.65–3.63 (2H, m, H-16), 3.05 (1H, dd, J=13.5, 4.1 Hz, H-3), 2.70–2.55 (1H, m, OH-1), 2.63 (1H, d, J=17.6 Hz, H-7), 2.24 (3H, s, Me-19), 2.06–1.98 (1H, m, H-2), 2.10–1.95 (1H, m, H-7), 1.92 (1H, dd, J=11.6, 1.7 Hz, H-5), 1.88–1.40 (2H, m, H-15), 1.78–1.67 (1H, m, H-2), 1.75–1.63 (2H, m, H-12), 1.74–1.65

(2H, m, H-11), 1.70–1.60 (1H, m, H-13), 1.39 (1H, d, J=11.6 Hz, H-5), 1.07 (3H, s, Me-20), 0.91 (3H, s, Me-18), 0.85 (3H, d, J=6.9 Hz, Me-17); ^{13}C NMR δ: 71.1 (C-1), 31.1 (C-2), 54.4 (C-3), 213.7 (C-4), 42.8 (C-5), 71.1 (C-6), 36.2 (C-7), 135.3 (C-8), 131.7 (C-9), 43.6 (C-10), 22.1 (C-11), 25.7 (C-12), 33.4 (C-13), 39.4 (C-14), 41.5 (C-15), 59.5 (C-16), 15.2 (C-17), 21.6 (C-18), 31.7 (C-19), 22.4 (C-20); EIMS: 336 (M^+, 1), 279 (15), 205 (10), 149 (40), 69 (100); EIHRMS: calcd for $C_{20}H_{32}O_4$ $(M)^+$ 336.2301, found $(M)^+$ 336.2310.

3.32. Saponification of 35 with K_2CO_3/MeOH: 39

To a solution of **35** (10 mg, 0.03 mmol) in MeOH (0.3 mL) K_2CO_3 (3.4 mg, 0.03 mmol) was added. The mixture was stirred at room temperature for 40 min. After that time, the reaction mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried (Na_2SO_4) and evaporated to give a crude mixture, which was purified by flash chromatography (hexane/EtOAc, 8:2 → 7:3) to give **39** (7 mg, 78%).

3.32.1. 1β-Acetoxy-16-hydroxy-8(18 → 14)-*abeo*-5-*epi*-picrasa-3,7-dien-6-one (39). $[\alpha]_D^{22}$ –2.4 (c 0.2, $CHCl_3$); IR (film): 3446, 1739, 1661, 1457, 1376, 1242, 1035 cm^{-1}; ^{1}H NMR δ: 5.87 (1H, s, H-7), 5.40 (1H, s, H-3), 5.05 (1H, t, J=2.0 Hz, H-1), 3.60–3.54 (1H, m, H-16), 3.39–3.28 (1H, m, H-16), 2.85 (1H, br s, H-5), 2.68 (1H, dd, J=11.2, 5.4 Hz, H-9), 2.64–2.55 (1H, m, H-2), 2.10–1.99 (1H, m, H-2), 2.06 (3H, s, MeCOO–), 2.05–2.00 (1H, m, H-15), 1.80–1.70 (1H, m, H-13), 1.70 (3H, s, Me-19), 1.58–1.40 (2H, m, H-12), 1.38–1.30 (1H, m, H-15), 1.30–1.22 (2H, m, H-11), 1.04 (3H, s, Me-18), 1.01 (3H, s, Me-20), 0.85 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR δ: 70.9 (C-1), 29.4 (C-2), 119.1 (C-3), 130.0 (C-4), 54.1 (C-5), 216.3 (C-6), 123.7 (C-7), 167.8 (C-8), 37.1 (C-9), 39.7 (C-10), 22.9 (C-11), 27.7 (C-12), 31.8 (C-13), 43.5 (C-14), 41.8 (C-15), 59.0 (C-16), 15.5 (C-17), 22.8 (C-18), 22.6 (C-19), 18.2 (C-20), 21.2 (*Me*COO–), 171.0 (Me*C*OO–); EIMS: 360 (M^+, 1), 205 (40), 178 (20), 151 (30), 119 (40); EIHRMS: calcd for $C_{22}H_{32}O_4$ $(M)^+$ 360.2301, found $(M)^+$ 360.2295.

3.33. Reduction of 28 with $LiAlH_4$: 40

An ice cooled solution of ketone **28** (12 mg, 0.03 mmol) in dry Et_2O (1 mL) was treated with $LiAlH_4$ (2 mg, 0.06 mmol) and was stirred at room temperature for 15 h. Then, the reaction mixture was cooled back to 0 °C and the excess of $LiAlH_4$ was decomposed by dropwise addition of wet EtOAc. Evaporation of the dried solution gave tetraol **40** (8 mg, 83%).

3.33.1. 8(18 → 14)-*abeo*-5-*epi*-Picras-7-en-1α,4β,6α,16-tetraol (40). IR (film): 3389, 1458, 1379, 1120, 1083, 1040 cm^{-1}; ^{1}H NMR δ: 5.47 (1H, s, H-7), 4.68 (1H, s, H-6), 3.75–3.65 (1H, m, H-1), 3.64 (2H, t, J=6.5 Hz, H-16), 2.15–0.90 (13H, m), 1.25 (3H, s, Me-19), 0.88 and 0.85 (3H, s each, Me-18, Me-20), 0.73 (3H, d, J=7.4 Hz, Me-17).

3.34. Reaction of 40 with Ac_2O/Py: 41

To a solution of **40** (8 mg, 0.02 mmol) in dry pyridine (1 mL) acetic anhydride (0.5 mL) was added and the mixture was stirred at room temperature for 3 days. The reaction mixture was poured into ice water and extracted with Et_2O. The organic layer was washed successively with aqueous 2 M HCl, aqueous 6% $NaHCO_3$ and water. The resulting solution was then dried (Na_2SO_4) and evaporated, obtaining a residue, which was purified by flash chromatography (benzene/acetone 95:5) to give **41** (8 mg, 73%).

3.34.1. 1α,6α,16-Triacetoxy-8(18 → 14)-*abeo*-5-*epi*-picras-7-en-4β-ol (41). $[\alpha]_D^{22}$ −6.7 (c 0.6, $CHCl_3$); IR (film): 3464, 1736, 1460, 1369, 1237, 1034, 665 cm^{-1}; ^{1}H NMR δ: 5.90 (1H, dd, J=3.8, 1.8 Hz, H-6), 5.91–5.89 (1H, m, H-6), 5.35 (1H, s, H-7), 4.71 (1H, dd, J=7.7, 4.4 Hz, H-1), 4.20–4.15 (1H, m, H-16), 4.12–4.05 (1H, m, H-16), 3.22–3.18 (1H, m, OH–), 2.68 (1H, dd, J=12.1, 2.2 Hz, H-9), 2.30–2.20 (1H, m, H-15), 2.13, 2.07 and 2.05 (3H, s each, MeCOO–), 2.10–0.90 (10H, m), 1.60–1.50 (1H, m, H-15), 1.28 (3H, s, Me-19), 1.07 (3H, s, Me-20), 1.05 (3H, s, Me-18), 0.81 (3H, d, J=6.4 Hz, Me-17); ^{13}C NMR δ: 72.3 (C-1), 25.1 (C-2), 37.4 (C-3), 72.5 (C-4), 53.3 (C-5), 81.6 (C-6), 120.8 (C-7), 169.9 (C-8), 35.6 (C-9), 41.5 (C-10), 23.2 (C-11), 28.4 (C-12), 35.3 (C-13), 42.4 (C-14), 40.7 (C-15), 61.8 (C-16), 15.6 (C-17), 23.5 (C-18), 24.1 (C-19), 21.9 (C-20), 21.7/21.3 (*Me*COO–), 27.1 (*Me*COOC-6), 172.2/171.5/171.4 (Me*C*OO–); EIMS: 464 (M^+, 1), 404 (10), 257 (5), 205 (20), 153 (30); EIHRMS: calcd for $C_{26}H_{40}O_7$ $(M)^+$ 464.2774, found $(M)^+$ 464.2766.

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