the mixture was stirred for 1 h, water (1 mL) was added at -70 °C. The mixture was poured into a mixture of 6 N HCl (5 mL) and EtOAc (20 mL). The aqueous layer was separated and extracted with EtOAc (30 mL × 2). The combined organic solution was washed with saturated NaCl, dried ($MgSO_4$), and then evaporated. The residue (0.49 g) was dissolved in EtOH (10 mL), and $NaBH_4$ (0.35 g, 9.3 mmol) was added to the solution. After being stirred at room temperature for 1.5 h, the mixture was poured into a mixture of 2 N HCl (20 mL) and EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (30 mL × 2). The combined organic solution was dried ($MgSO_4$) and evaporated. The residue was heated in benzene (15 mL) containing *p*-toluenesulfonic acid (40 mg) with a Dean-Stark apparatus for 30 min. The benzene solution was washed successively with saturated $NaHCO_3$ and saturated NaCl. After drying ($MgSO_4$), evaporation gave (-)-**26** (0.17 g, 24%): $[\alpha]^{18}_D$ -27.8° (*c* 3.05, MeOH); ^1H NMR (200 MHz) δ 1.48-1.68 (m, 1 H), 1.82-1.96 (m, 2 H), 1.96-2.18 (m, 1 H), 2.20-2.40 (m, 1 H), 2.49-2.70 (m, 2 H), 4.25-4.39 (m, 2 H), 5.03-5.19 (m, 2 H), 5.73-5.94 (m, 1 H); HRMS *m/z* (M^+) calcd for $C_8H_{12}O_2$ 140.0837, found 140.0867.

4-(Hydroxymethyl)-6-heptenenitrile (27). To a solution of (-)-**24** ($[\alpha]^{15}_D$ -13.8°, 1.45 g, 9.5 mmol) in ether (5 mL) was added an ethereal solution of diazomethane. After evaporation, the residue was dissolved in dry EtOH (130 mL) and heated with LiCl (1.6 g, 3.8 mmol) and $NaBH_4$ (1.45 g, 3.8 mmol) at 50 °C for 10 h. After filtering off inorganic materials, the solution was evaporated. The residue was dissolved in CH_2Cl_2 (100 mL), and the solution was washed successively with 2 N HCl, saturated $NaHCO_3$, and saturated NaCl. After drying ($MgSO_4$), evaporation gave **27** as an oil (1.14 g, 86%): ^1H NMR (200 MHz) δ 1.60-1.87 (m, 3 H), 2.06-2.18 (m, 2 H), 2.45 (t, *J* = 7.0 Hz, 2 H), 3.46-3.73 (m, 2 H), 5.00-5.20 (m, 2 H), 5.64-5.80 (m, 1 H).

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-7-hydroxyheptanenitrile (28). To a mixture of **27** (1.13 g, 8.11 mmol) and imidazole (0.66 g, 9.7 mmol) in dry CH_2Cl_2 (13 mL) was added *tert*-butyldimethylsilyl chloride (1.5 g, 9.7 mmol) under ice cooling. After being stirred at room temperature for 24 h, the mixture was washed successively with water and saturated NaCl. The solution was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (18% EtOAc in hexane) to give the silyl ether (1.56 g, 76%).

To a solution of this silyl ether (1.56 g, 6.14 mmol) in dry THF (6 mL) was added a THF solution of 9-BBN (0.5 M, 14.7 mL, 7.4 mmol) at room temperature. After the mixture was stirred for 1.5 h, water (0.3 mL) and 30% H_2O_2 (2.1 mL) were added successively below 50 °C. Then 3 N NaOH (2.1 mL) was added to the mixture. After being stirred at room temperature for 1 h, the mixture was diluted with ether (100 mL). The organic layer was separated and washed with saturated NaCl. The solution was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (36% EtOAc in hexane) to give **28** as an oil (1.24 g, 75%): ^1H NMR (200 MHz) δ 0.04 (s, 6 H), 0.80 (s, 9 H), 1.12-1.80 (m, 8 H), 2.34 (t, *J* = 7.2 Hz, 2 H), 3.36-3.66 (m, 4 H).

7-(Benzyloxy)-4-(hydroxymethyl)heptanenitrile (29). A solution of **28** (1.22 g, 4.5 mmol) in dry THF (5 mL) was added dropwise to a solution of Bu^tOK (0.61 g, 5.4 mmol) in dry THF (3.5 mL). After the mixture was stirred at room temperature for 5 min, benzyl bromide (0.93 g, 5.4 mmol) was added. The mixture was stirred at room temperature for 10 h and then diluted with water (20 mL). The mixture was extracted with ether (30 mL × 3), and the combined extracts were washed with saturated NaCl and dried ($MgSO_4$). After evaporation, the residue was purified by flash chromatography (18% EtOAc in hexane) to give the benzyl ether as an oil (1.18 g, 72%).

This benzyl ether (1.15 g, 3.18 mmol) was dissolved in dioxane (25 mL) and treated with 6 N H_2SO_4 (2.5 mL) at room temperature overnight. The mixture was diluted with water (50 mL) and extracted withe ether (50 mL × 3). The combined extracts were washed successively with saturated $NaHCO_3$ and saturated NaCl and then dried ($MgSO_4$). Evaporation gave **29** as an oil (0.69 g, 87%): ^1H NMR (200 MHz) δ 1.32-1.48 (m, 2 H), 1.54-1.88 (m, 5 H), 2.41 (t, *J* = 7.0 Hz, 2 H), 3.48 (t, *J* = 6.2 Hz, 2 H), 3.52-3.70 (m, 2 H), 4.50 (s, 2 H), 7.33 (s, 5 H).

(-)-4-(3-Hydroxypropyl)-5-pentanolide [(-)-23]. To a solution of **29** (0.67 g, 2.7 mmol) in EtOH (10 mL) was added a solution of KOH (4.5 g, 81 mmol) in water (5 mL). The mixture was heated at 50 °C for 8 h and then diluted with water (30 mL). After being washed with ether, the aqueous solution was made acidic with 6 N HCl and extracted with EtOAc (50 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was heated in benzene (30 mL) containing *p*-toluenesulfonic acid (70 mg) with a Dean-Stark apparatus for 30 min. The benzene solution was washed successively with saturated $NaHCO_3$ and saturated NaCl. After drying ($MgSO_4$), the solution was evaporated. The residue was purified by flash chromatography (56% EtOAc in hexane) to give the protected lactone (0.53 g, 80%): $[\alpha]^{20}_D$ -2.7° (*c* 5.2, EtOH).

This protected lactone (0.20 g, 0.81 mmol) was dissolved in EtOAc (4 mL) and hydrogenated over 26% $Pd(OH)_2/C$ (0.2 g) under ambient pressure at room temperature for 2 h. The mixture was filtered, and the filtrate was evaporated to give (-)-**23** (0.122 g, 95%) as an oil: $[\alpha]^{20}_D$ -3.1° (*c* 5.05, EtOH).

Acknowledgment. This work was supported in part by a grant in aid for scientific research on a priority area, advanced molecular conversion, and a grant (63470117) from the Ministry of Education of Japan to which we are deeply grateful.

Supplementary Material Available: Experimental details for synthesis and lactonization of the cyclic amide alcohol **6c** and the linear amide alcohols **14a,b** and **15a,b** as well as detailed results of the MM2 calculation including the parameters used herein plus ^1H and/or ^{13}C NMR spectra for most all compounds (52 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Amarolide, a Quassinoid Bitter Principle

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The first total synthesis of amarolide (1), a bitter tasting quassinoid having a picrasane skeleton with 10 chiral centers, is described in racemic form. The synthesis of (±)-1 was accomplished stereoselectively in 35 steps and 0.5% overall yield from a known tricyclic compound **7**. An orthoester Claisen rearrangement and a lead tetraacetate oxidation were utilized as key reactions to prepare hydroxy ketone **14** with a complete picrasane skeleton. This hydroxy ketone was transformed into 1 in 18 steps that included 1,3-carbonyl transposition, introduction of hydroxyl groups at C-2 and C-11 positions, and oxidation of an ether to afford a δ-lactone.

Quassinoid is a generic name for terpenoids represented by amarolide (1), quassin (2), and so on, that have been isolated from plants of Simaroubaceae family.[1] Most of these quassinoids have a bitter taste, and some of them

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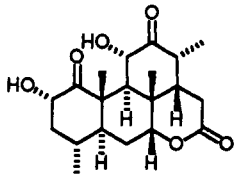
show remarkable biological activities such as cytotoxic and antineoplastic effects. The chemical structures of these quassinoids possess a picrasane skeleton (3) or a variant thereof. Reports on the complete total synthesis of quassinoids have been very few,[2-6] because of their highly oxygenated carbon skeletons and their complex stereochemical arrangements. Numerous synthetic efforts[7] reflect continued interest in the synthesis and biological evaluation of these quassinoids. With the exception of our communication[2] and a very recent report by Watt's group,[6] only Grieco's group has finished complete total syntheses of (±)-quassin (2),[3] (±)-castelanolide (4),[4] and (±)-klaineanone (5),[5] via intermolecular Diels–Alder reactions. Amarolide (1) was first isolated from *Ailanthus glandulosa* as a bitter principle,[8] and we reported the isolation of this quassinoid from *A. altissima*.[9] We now report a stereoselective total synthesis of (±)-amarolide (1).[2]



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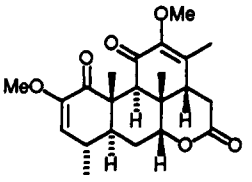

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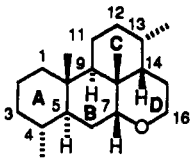

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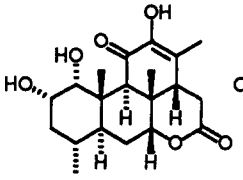

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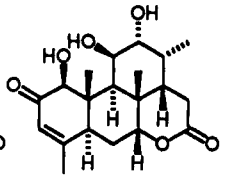
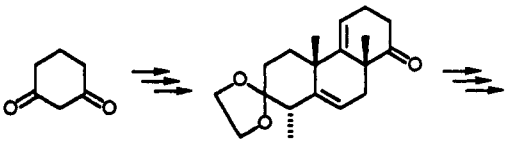


5

One of us has previously reported the synthesis of 14α*H*-5-picrasene-type compound (6)[10,11] from cyclohexane-1,3-dione via the readily available tricyclic ketone 7.[12] In the synthesis shown in Scheme I, however, several severe hurdles needed to be overcome. First, nucleophilic attack at C-14 position of diketone 8, which was one of the key reactions in the planned synthesis, led to poor yields because of steric hindrance. Only the dianion of acetic acid

Scheme I



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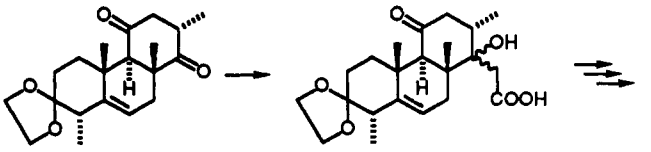

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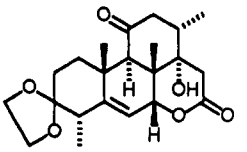

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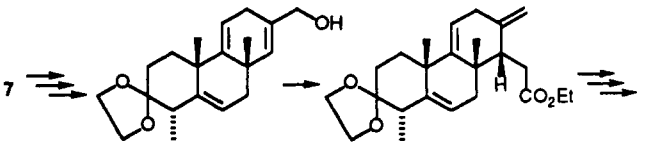
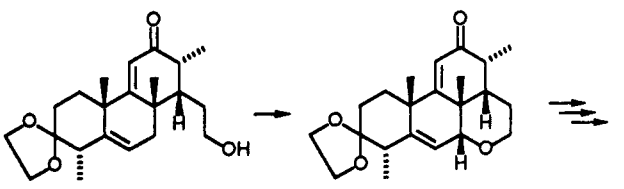
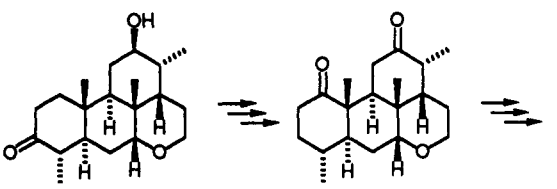
Scheme II



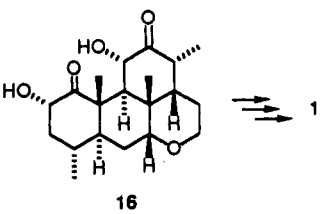
10 11



12 13



14 15



16 1

proved useful in providing a mixture of diastereomers (9) at C-14, and, unfortunately, the natural-type diastereomer was the minor product. Secondly, an allylic oxidation at C-7 of the methyl ester derivative of 9 proceeded in poor yield.

We devised a regio- and stereoselective total synthetic plan for (±)-amarolide (1), with the goal of overcoming these severe problems. The same tricyclic ketone (7) would be used as the starting material; however, the utilization of intramolecular reactions, instead of intermolecular ones, would introduce the two-carbon unit at C-14 and some oxygen functional group at C-7 stereospecifically. A compound possessing the "complete" picrasane-type skeleton with the correct chiral centers at all the angular positions would be prepared, and the transposition and the intro-

(1) For reviews on quassinoids, see: Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 22; **1973**, *30*, 101.

(2) For the preliminary accounts of this work, see: Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 435. Miyaji, K.; Nakamura, T.; Hirota, H.; Igarashi, M.; Takahashi, T. *Ibid.* **1984**, *25*, 5299.

(3) Grieco, P. A.; Ferrino, A.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. Vidari, G.; Ferrino, A.; Grieco, P. A. *Ibid.* **1984**, *106*, 3539.

(4) Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601. Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *Ibid.* **1984**, *49*, 2342.

(5) (a) Grieco, P. A.; Parker, D. T.; Nargund, R. P. *J. Am. Chem. Soc.* **1988**, *110*, 5568. (b) Grieco, P. A.; Nargund, R. P.; Parker, D. T. *Ibid.* **1989**, *111*, 6287.

(6) Kim, M; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504.

(7) See the ref 3 in ref 5b, and references cited in ref 6.

(8) Casinovi, C. G.; Bellavita, V.; Grandolini, G.; Ceccherelli, P. *Tetrahedron Lett.* **1965**, 2273. Stocklin, W.; Stefanovic, M.; Geissman, T. A.; Casinovi, C. G. *Ibid.* **1970**, 2399.

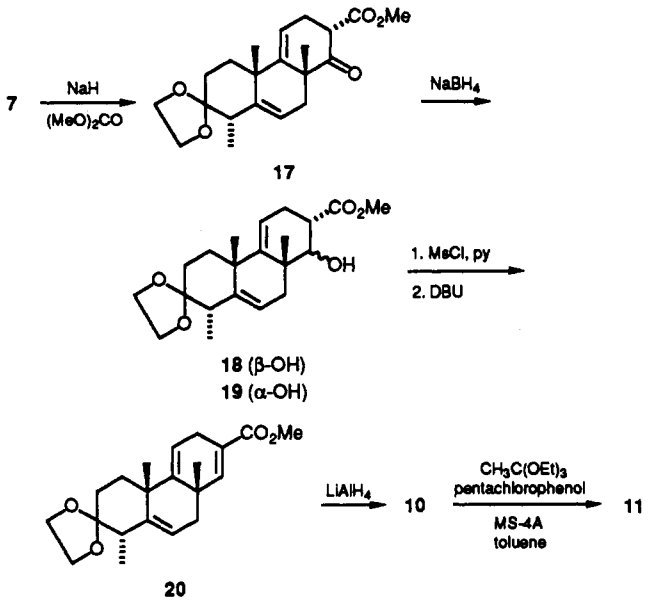
(9) Ishibashi, M.; Murae, T.; Hirota, H.; Naora, H.; Tsuyuki, T.; Takahashi, T.; Itai, A.; Iitaka, Y. *Chem. Lett.* **1981**, 1597. Ishibashi, M.; Tsuyuki, T.; Murae, T.; Hirota, H.; Takahashi, T.; Itai, A.; Iitaka, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3683.

(10) Honda, T.; Murae, T.; Ohta, S.; Kurata, Y.; Kawai, H.; Takahashi, T.; Itai, A.; Iitaka, Y. *Chem. Lett.* **1981**, 299.

(11) Numbering of the compounds described in the main text is adopted from those of the picrasane skeleton (3). All the synthetic compounds are racemic; only one enantiomer is shown for convenience.

(12) This tricyclic ketone (7) was also utilized for the synthesis of labdane-type diterpenoids: Nakamura, T.; Hirota, H.; Takahashi, T. *Chem. Pharm. Bull.* **1986**, *34*, 3518. Hirota, H.; Nakamura, T.; Tsuyuki, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4023.

Scheme III



duction of oxygen functional groups would afford the final compound 1 stereoselectively.

For convenience, the whole synthetic pathway is shown in Scheme II. Results and discussions on each synthetic stage are detailed below.

Synthesis of Ester 11 via Stereospecific Introduction of Two-Carbon Unit at C-14 (Orthoester Claisen Rearrangement). In order to introduce a two-carbon unit at C-14 of a derivative of tricyclic ketone **7**, we decided to apply the Claisen rearrangement method[13] to a derivative of allylic alcohol **10**. A derivative with C-14βH like **11** would be produced stereoselectively from allylic alcohol **10**, because the β-side of the double bond between C-13 and C-14 was expected to be more sterically hindered than the α-side.

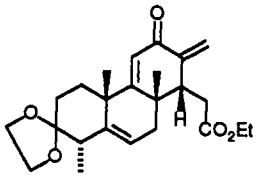
Allylic alcohol **10** was obtained from ketone **7** via the 5-step reaction sequence shown in Scheme III in 82% yield. In this sequence, two epimeric alcohols (**18** and **19**) were obtained in a 6/1 ratio (14β-OH/14α-OH) from the reduction of **17**.[14] The conjugated ester **20** was obtained in almost the same yield from both epimers (**18** and **19**), even though the individual reaction rates were fairly different.

The enolate Claisen rearrangement procedure[15] was first applied to the acetate of allylic alcohol **10** without success. Then, an orthoester Claisen rearrangement reaction was applied to **10** by heating with triethyl orthoacetate in the presence of acid catalyst under various reaction conditions.[13,16] When a mixture of **10** and triethyl orthoacetate in toluene was heated under reflux in the presence of pentachlorophenol and 4-Å molecular sieves, the desired rearranged product **11** with the correct C-14βH stereochemistry was obtained in 53% yield (88% yield in consideration of recovered starting material). The stereochemistry of **11** was determined by NOE experiments with a tetracyclic compound (**30**) mentioned later. When propionic acid or pivalic acid was used instead of pentachlorophenol as the catalyst, only the corresponding ester of **10** could be obtained. When 2,4-dinitrophenol was used, a complex product mixture was obtained even though the production of some **11** could be detected.

Construction of D Ring Using Lead Tetraacetate (Preparation of 13). When triene ester **11** was treated with chromium(VI) reagents such as Collins reagent or *tert*-butyl chromate,[17] only the trienone **21** was obtained; thus, allyl oxidation occurred at C-12 instead of C-7. An intramolecular oxidation at C-7 was, therefore, investigated as mentioned earlier. The plan was as follows: the lead tetraacetate oxidation reaction was to be applied to a derivative such as **12** and **22** with a hydroxyethyl (primary hydroxyl) group instead of an ester group at C-14. The reaction would proceed via the intramolecular abstraction of a hydrogen at C-7 as a radical and an ether ring corresponding to the D ring would be formed.

When alcohol **22** obtained by reduction of **11** with lithium aluminum hydride was treated with lead tetraacetate, a complex mixture was obtained. This result evidently reflected the presence of the very reactive *exo*-methylene moiety at C-13 and the presence of two allylic positions (C-7 and C-12) that could each afford a six-membered ether ring. Consequently, a compound which possesses methyl group at C-13 instead of the *exo*-methylene group and whose reactivity at C-12 is lower than that at C-7 was considered to be a more suitable substrate for the oxidative cyclization.

Selective reduction of the *exo*-methylene group of trienone **21** (obtained by allylic oxidation of **11**) using platinum oxide afforded **23** regio- and stereospecifically. When **23** was reduced with lithium aluminum hydride, two diastereomeric alcohols (**24** and **25**) were obtained in poor yields, because of side reactions such as dehydration. Separate treatment of **24** and **25**, respectively, with lead tetraacetate afforded only complex mixtures, possibly as a result of the high reactivity of the C-12 hydroxyl group. Several attempts to protect of the C-12 hydroxyl group of compounds **23**, **24**, and **25** were, however, unproductive.



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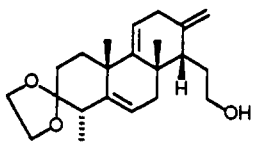

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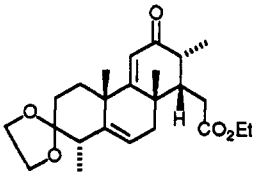
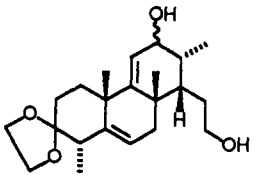


23



24 + 25

It became necessary to incorporate protection and deprotection operation at the cost of several additional steps. Triene ester **11** was converted into keto alcohol **12** in five steps and 31% yield as shown in Scheme IV. That is, the hydroxyl group of allylic alcohol **22** was protected as the acetate **26**, and the C-12 position of **26** was oxidized to furnish **27**. The *exo*-methylene group of **27** was hydrogenated over platinum oxide regio- and stereospecifically

(13) For reviews on Claisen rearrangement reactions, see: Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. Bennett, B. *Synthesis* **1977**, 589.

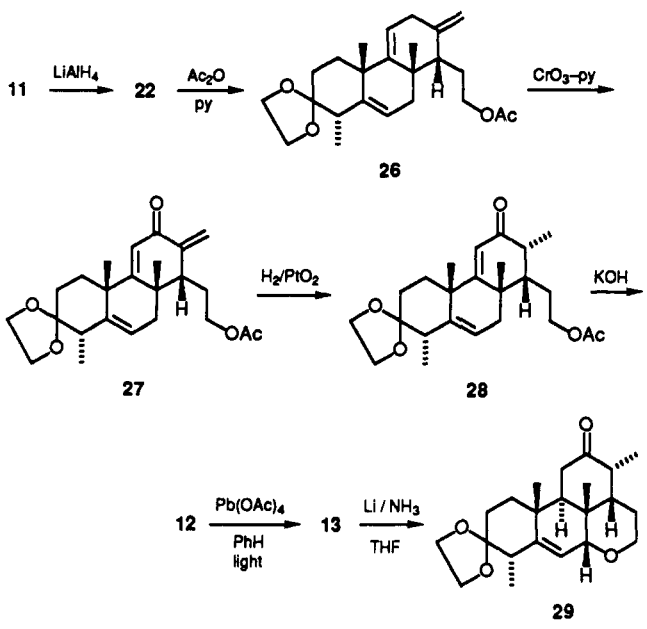
(14) The stereochemistry at C-14 of **18** and **19** was confirmed by ^{1}H NMR coupling constants of 14-Hs of their acetates; that is $\delta_{14\text{-H}}$ 5.06 (d, J = 11 Hz) on the acetate of major isomer (**18**), and $\delta_{14\text{-H}}$ 5.23 (s) on that of minor one (**19**).

(15) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(16) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(17) Cr(VI) oxidative ring closure has been reported: Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org. Chem.* **1984**, *49*, 3264.

Scheme IV



to afford 28, and hydrolysis of the acetate group of 28 gave 12.

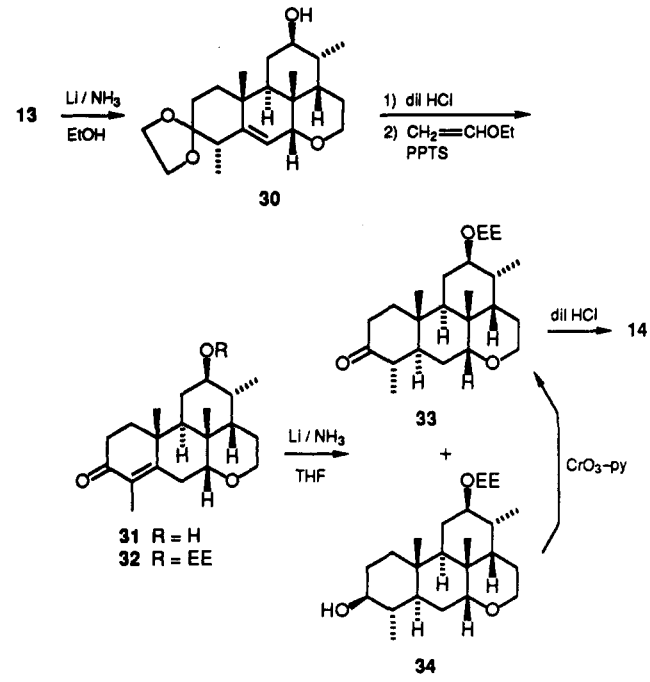
When keto alcohol 12 was treated with lead tetraacetate in benzene under irradiation with visible light, a tetracyclic compound (13) was obtained in 52% yield (78% based on recovered starting material). The stereochemistry at C-7, C-13, and C-14 of this ether (13) was determined to be all β-H orientation by NOE experiments on the ketone 29 obtained by Birch reduction of conjugated ketone 13. That is, when C-8β methyl protons were irradiated, no signal enhancement was observed at the C-9 methine proton, suggesting the C-9αH disposition, but the methine protons at C-7, C-13. and C-14 showed 7%, 9%, and 7% NOE enhancements, respectively, indicating the β-orientation for all these methine protons.

Construction of Compound 14 with the "Complete" Picrasane Skeleton. A compound with the "complete" picrasane skeleton, with the correct relative stereochemistry at all six angular chiral centers would be prepared from the tetracyclic ether 13 via hydrolysis of the acetal followed by Birch reduction of both enones. To complete the total synthesis of amarolide (1), however, it was necessary to differentiate the reactivity or functionality at C-3 from that at C-12. Toward this end, the 3-keto-12β-alcohol (14) with a "complete" picrasane skeleton was prepared via five-step sequence (13 → 30 → 31 → 32 → 33 → 14) in 52% yield as shown in Scheme V. Unfortunately, lithium–ammonia reduction of enone 31 gave both keto alcohol 14 and the 3β,12β-diol which was unsuitable for the following transformations. However, after protection of the 12β-hydroxyl group of 31 as an ethoxyethyl ether, Birch reduction afforded ketone 33 as the major product and alcohol 34 as a minor product. The latter 34 was transformed into ketone 33 by oxidation.

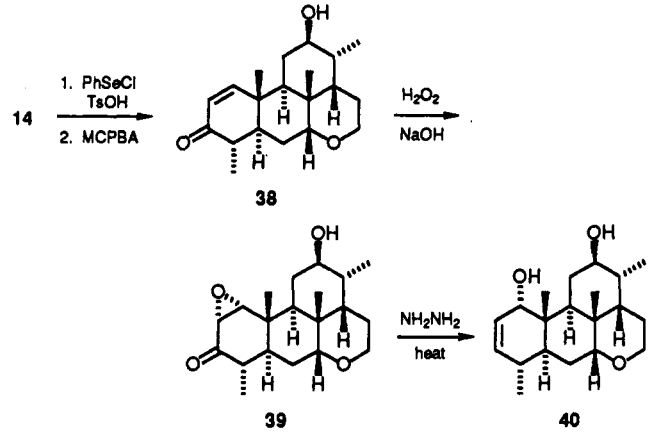
By means of 400-MHz ^{1}H NMR spectra (including decoupling experiments) of keto alcohol 14 in the presence of the shift reagent Eu(fod)$_3$-d_{27}, the stereochemistry of the three chiral centers (C-4, C-5, and C-12) newly formed by these Birch reductions were determined to be C-4βH, C-5αH, and C-12αH as expected.

Carbonyl 1,3-Transposition (Preparation of Picrasane-1,12-dione (15)). Following the original plan for the synthesis of amarolide (1) from 12β-hydroxypicrasan-3-one (14), it was necessary to transpose the C-3 carbonyl group

Scheme V

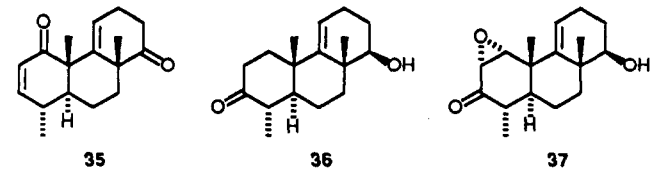


Scheme VI



of 14 to C-1 prior to the introduction of hydroxyl groups at C-2 and C-11 and the oxidation of the D-ring ether into the lactone.

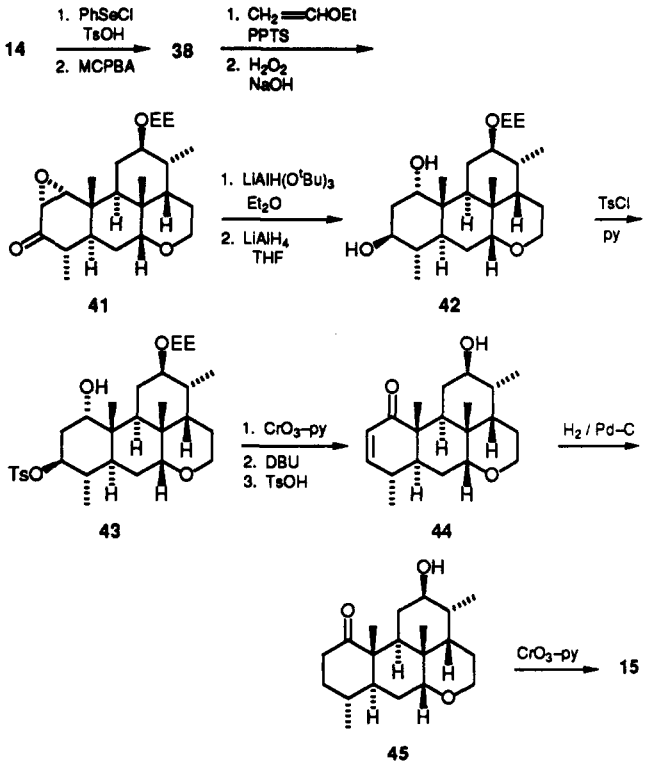
Various methods had been reported for the 1,3-transposition reaction of carbonyl group,[18] and we have previously reported[19] the preparation of a tricyclic diketone (35) from the hydroxy ketone 36 via epoxy ketone 37 in



fair yield utilizing the Wharton reaction.[20] Keto alcohol 14 was transformed via conjugated ketone 38 into α,β-epoxy ketone 39 in three steps and 59% yield as shown in

(18) Morris, D. G. *Chem. Soc. Rev.* **1982**, *11*, 397.
(19) Kurata, Y.; Hirota, H.; Honda, T.; Takahashi, T. *Chem. Pharm. Bull.* **1987**, *35*, 837.
(20) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. Koch, H. J.; Pfenninger, H.; Graf, W. *Helv. Chim. Acta* **1975**, *58*, 1727.

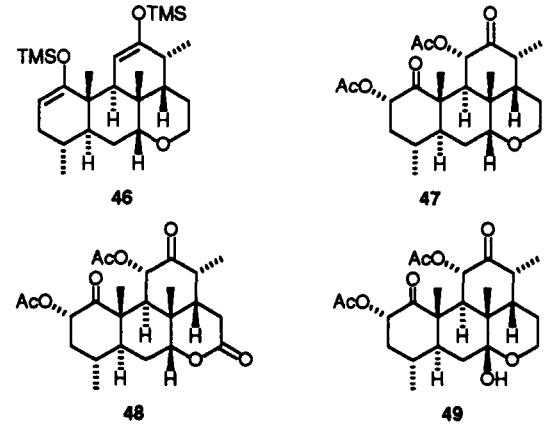
Scheme VII



Scheme VI. However, when **39** was heated with hydrazine, the Wharton reaction product **40** could be isolated only in at most 26% yield from the complex reaction mixture because of the drastic reaction conditions.

Another 1,3-carbonyl transposition reaction pathway shown in Scheme VII was therefore considered.[21] Although this pathway was longer, the overall yield was better, and the reaction conditions were milder than those in Scheme VI. α,β-Epoxy ketone **41**, prepared from **14** via **38** in four steps (52% yield, including the protection of a hydroxyl group at C-12), was reduced to 1α,3β-diol **42** in two steps in 85% yield with more than 90% stereoselectivity. The 3β-hydroxyl group of **42** was converted to the tosylate **43** regiospecifically because of the steric hinderance of 1α-hydroxyl group. The 1α-hydroxyl group of **43** was oxidized into a carbonyl group followed by elimination of tosic acid and deprotection of ethoxyethyl ether at the C-12 hydroxyl group to afford 12β-hydroxypicras-2-en-3-one (**44**) in 90% yield from **42**. Picrasane-1,12-dione (**15**) was obtained in 99% yield from **44** via keto alcohol **45** by hydrogenation and Collins oxidation reactions.

Preparation of 2α,11α-Dihydroxypicrasane-1,12-dione (16). Simultaneous introduction of two hydroxyl groups adjacent to the two carbonyl groups of **15** was next examined. When **15** was treated with 2 equiv of lithium diisopropylamide (LDA) followed by the addition of a large excess amount of molybdenum peroxide complex (MoO_5·py·HMPA),[22] only the monohydroxyl derivative (probably 2α-hydroxyl one) was obtained. The bis(trimethylsilyl) enol–ether **46** of **15** was therefore trapped with trimethylsilyl chloride after treatment of the diketone **15** with 2 molar equiv of LDA. The enol–ether **46** was oxidized with peracid followed by acid treatment to afford the desired dihydroxy dione derivative **16** in 65% yield from **15**. The configuration of both hydroxyl groups was determined to be α-equatorial from the coupling constants of the C-2 and C-11 protons and the transformation of this compound **16** into (±)-amarolide (**1**) as described below.



Oxidation of the Ether into the Lactone (Transformation into (±)-Amarolide (1)). Ruthenium tetraoxide was used in the final total synthetic stage for the conversion of the tetrahydropyran ring into the δ-lactone. Before the reaction, the two hydroxyl groups of **16** were protected by acetylation in 90% yield. When this diacetate (**47**) was treated with stoichiometric amounts of ruthenium tetraoxide in carbon tetrachloride,[23] (±)-amarolide diacetate (**48**) was obtained in 27% yield, together with a compound that might possess a hydroxyl group at C-7 as in **49**. The poor regioselectivity in this oxidation reaction could not be improved even on addition of acetonitrile[24] and by several other changes in the conditions.

Finally, acid hydrolysis of the diacetate **48** afforded (±)-amarolide (**1**) in 87% yield. The synthetic (±)-amarolide was shown to be identical with our natural sample by comparison of their 270-MHz ^1H NMR spectra. ^1H and ^{13}C NMR spectra of the synthetic amarolide diacetate are also identical with those of the diacetyl derivative of natural amarolide. Amarolide diacetate **48** has also been isolated from a Simaroubaceae plant as a natural compound.[25]

The total synthesis of (±)-amarolide (**1**) was accomplished in 35 steps and 0.5% overall yield from the known ketone **7** as shown in Scheme II. As the transformation of amarolide (**1**) into quassin (**2**) was already reported,[8] this synthesis also constitutes a formal total synthesis of (±)-quassin (**2**).

Experimental Section

General Information. All melting points were measured on a capillary melting point apparatus (Laboratory Devices) and were uncorrected. Mass spectra (MS) were run at 70 eV. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 GF_{254} (0.25 mm thickness). Wakogel C-200 (Wako) was used for silica gel column chromatography.

Methyl 2-(Ethylenedioxy)-1α,4aβ,8aβ-trimethyl-8-oxo-1,2,3,4,4a,6,7,8,8a,9-decahydrophenanthrene-7α-carboxylate (17). A mixture of NaH (60% in oil; 9.63 g, 240 mmol) and KH (50% in oil; 1.93 g, 24 mmol)[26] was washed with hexane (30 mL).

(21) Reduction of 1α,2α-epoxy-3-keto steroids into 1α,3β-dihydroxyl derivatives has been reported, e.g.: Morisaki, M.; Bannai, K.; Ikekawa, N. *Chem. Pharm. Bull.* **1973**, *21*, 1853. Rubio-Lightbourn, J.; Morisaki, M.; Ikekawa, N. *Ibid.* **1973**, *21*, 1854. Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Rizzardo, E. *J. Chem. Soc., Chem. Commun.* **1974**, 203.

(22) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(23) Smith, A. B. III; Scarborough, R. M., Jr. *Synth. Commun.* **1980**, *10*, 205.

(24) Carlsen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(25) Ghosh, P. C.; Larrahondo, J. E.; Le Quesne, P. W.; Raffauf, P. E. *Lloydia* **1977**, *40*, 364.

To the mixture were added dry dimethoxyethane (DME; 150 mL), dimethyl carbonate (25.3 mL, 300 mmol), and a solution of tricyclic ketone 7 (18.17 g, 60 mmol) in DME (300 mL) successively. This mixture was refluxed under N_2 for 1 h. After addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with ether four times. The ether solution was dried over ($MgSO_4$). Purification by silica gel (150 g) column chromatography (3% acetone in benzene) afforded keto ester 17 (21.65 g; 100%) as white crystals: mp 103–105 °C (from benzene); IR (KBr) 1680, 1650, 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.01 (3 H, d, J = 6 Hz), 1.35 (3 H, s), 1.40 (3 H, s), 2.90 (2 H, br d, J = 4.5 Hz), 3.77 (1 H, s, OMe), 3.8–4.0 (4 H, m), 5.43 (1 H, m), 5.59 (1 H, t, J = 4.5 Hz), 12.25 (1 H, s, enolic OH); MS m/z (%) 360 (M^+, 2), 329 (0.5), 99 (100); found m/z 360.1937, calcd for $C_{21}H_{28}O_5$ (M) 360.1937.

Methyl 2-(Ethylenedioxy)-8β-hydroxy-1α,4aβ,8aβ-trimethyl-1,2,3,4,4a,6,7,8,8a,9-decahydrophenanthrene-7α-carboxylate (18) and Its 8α-Hydroxyl Derivative (19). To a solution of keto ester 17 (1.27 g, 3.52 mmol) in dry ethanol (100 mL) was added $NaBH_4$ (135 mg, 3.57 mmol), and the mixture was stirred at 0 °C for 3 h under N_2 followed by addition of acetone (2 mL) and saturated aqueous NH_4Cl (20 mL). After evaporation of the organic solvents, the aqueous mixture was extracted with $CHCl_3$ (3 times), dried ($MgSO_4$), and purified by silica gel (50 g) column chromatography (3% acetone in benzene) to afford hydroxy esters 18 and 19. From the less polar fractions, β-hydroxy ester 18 was obtained as white crystals (890 mg; 70%): mp 145.5–146.5 °C (from benzene); IR (KBr) 3500, 1720 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (3 H, d, J = 7 Hz), 1.13 (3 H, s), 1.31 (3 H, s), 3.74 (3 H, s), 3.8–4.0 (5 H, m), 5.45 (2 H, m); MS m/z (%) 362 (M^+, 3.2), 344 (0.2), 331 (0.7), 99 (100); found m/z 362.2063, calcd for $C_{21}H_{30}O_5$ (M) 362.2093. From the more polar fractions, α-hydroxy ester 19 was obtained as white crystals (154 mg; 12%): mp 182–183.5 °C (from benzene); IR (KBr) 3480, 1735 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (3 H, d, J = 7 Hz), 1.17 (3 H, s), 1.29 (3 H, s), 3.73 (3 H, s), 3.8–4.0 (5 H, m), 5.46 (1 H, m), 5.59 (1 H, m); MS m/z (%) 362 (M^+, 4.5), 331 (1), 99 (100); found m/z 362.2102, calcd for $C_{21}H_{30}O_5$ (M) 362.2094.

Methyl 2-(Ethylenedioxy)-1α,4aβ,8aβ-trimethyl-1,2,3,4,4a,6,8a,9-octahydrophenanthrene-7-carboxylate (20). A solution of hydroxy ester 18 (272 mg, 0.75 mmol) in dry CH_2Cl_2 (20 mL), dry pyridine (1.3 mL), and methanesulfonyl chloride (0.6 mL, 7.7 mmol) was stirred under N_2 at room temperature for 2 days. After addition of methanol (1 mL), the mixture was washed with saturated aqueous $NaHCO_3$ three times and water twice, successively, and was dried ($MgSO_4$). After evaporation, the residual oil was dissolved in dry tetrahydrofuran (THF; 25 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (3 mL) was added, and the solution was refluxed for 18 h under N_2. Saturated aqueous NH_4Cl was added, and the reaction mixture was extracted with ether three times. The ether solution was dried ($MgSO_4$). Purification by silica gel (8 g) column chromatography (3–5% acetone in benzene) afforded α,β-unsaturated ester 20 (260 mg; 100%) as white crystals: mp 112–113 °C; IR (KBr) 1715, 1640 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (3 H, d, J = 7 Hz), 1.24 (3 H, s), 1.33 (3 H, s), 2.91 (2 H, br d, J = 14 Hz), 3.71 (3 H, s), 3.8–4.0 (4 H, m), 5.36 (1 H, m), 5.60 (1 H, t, J = 4 Hz), 6.59 (1 H, s); MS m/z (%) 344 (M^+, 2.9), 313 (0.6), 99 (100). Anal. Found: C, 72.98; H, 8.17; m/z 344.1981. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19; (M) 344.1986. When α-hydroxyl ester 19 was used instead of 18, mesylation reaction took for only 4 h at room temperature, and the elimination of methanesulfonic acid required only 1 h under reflux, affording the same α,β-unsaturated ester (20) in almost quantitative yield.

2-(Ethylenedioxy)-1α,4aβ,8aβ-trimethyl-1,2,3,4,4a,6,8a,9-octahydrophenanthrene-7-methanol (10). To a solution of ester 20 (148 mg, 0.43 mmol) in dry THF (10 mL) was added $LiAlH_4$ (40 mg, 1.05 mmol), and the mixture was stirred at 0 °C for 35 min. After addition of ethyl acetate, water, and 2 M HCl, successively, the mixture was extracted with ether three times. The ether layer was washed twice with saturated aqueous $NaHCO_3$ and once with saturated aqueous NaCl and was dried ($MgSO_4$). After removal of solvent, the residue was purified on silica gel (10 g) column chromatography (10–20% acetone in benzene) to afford allylic alcohol 10 (136 mg; 100%) as white crystals: mp 108.5–111 °C (benzene); IR (KBr) 3400, 1640 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.02 (3 H, d, J = 6 Hz), 1.18 (3 H, s), 1.32 (3 H, s), 2.70 (2 H, br d, J = 4 Hz), 3.8–3.95 (4 H, m), 4.02 (2 H, s), 5.35 (2 H, m), 5.59 (1 H, t, J = 4 Hz); MS m/z (%) 316 (M^+, 1.5), 301 (0.4), 99 (100). Anal. Found: C, 75.73; H, 8.89; m/z 316.2021. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; (M) 316.2039.

Ethyl 2-(Ethylenedioxy)-1α,4aβ,8aβ-trimethyl-7-methylene-1,2,3,4,4a,6,7,8,8a,9-decahydrophenanthrene-8α-acetate (11). A solution of allylic alcohol 10 (226 mg, 0.715 mmol) in toluene (40 mL), ethyl orthoacetate (6 mL, 32 mmol), and pentachlorophenol (75 mg, 0.28 mmol) was refluxed for 10 h with a Dean–Stark trap filled with 4-Å molecular sieves. After addition of benzene (40 mL), the mixture was washed with saturated aqueous $NaHCO_3$ twice and was dried ($MgSO_4$). Purification by silica gel column chromatography (0.5% acetone in benzene) afforded recovered 10 (90 mg; 40%) and Claisen rearrangement product 11 (146 mg; 53%): oil; IR (neat) 1740, 1655 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (3 H, d, J = 6 Hz), 1.14 (3 H, s), 1.20 (3 H, t, J = 7 Hz), 1.27 (3 H, s), 3.8–3.95 (4 H, m), 4.05 (2 H, q, J = 7 Hz), 4.74 (2 H, br s), 5.4–5.6 (2 H, m); MS m/z (%) 386 (M^+, 6.2), 371 (1.5), 341 (1.3), 99 (100); found m/z 386.2462, calcd for $C_{24}H_{34}O_4$ (M) 386.2458.

2-(Ethylenedioxy)-7-methylene-1α,4aβ,8aβ-trimethyl-1,2,3,4,4a,6,7,8,8a,9-decahydrophenanthrene-8α-ethanol (22). To a solution of ester 11 (120 mg, 0.31 mmol) in dry THF (40 mL) was added $LiAlH_4$ (100 mg, 2.63 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h under N_2. After addition of ethyl acetate followed by a mixture of ether and water, the mixture was extracted with ether three times and was dried ($MgSO_4$). Purification by silica gel (10 g) column chromatography (20% ether in benzene) afforded the alcohol 22 (77 mg; 72%) as an oil: IR (neat) 3600–3100 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.99 (3 H, d, J = 7 Hz), 1.10 (3 H, s), 1.25 (3 H, s), 3.53 (2 H, t, J = 6 Hz), 3.8–4.2 (4 H, m), 4.7–5.0 (2 H, m), 5.5 (2 H, m); MS m/z (%) 344 (M^+, 3.6), 300 (1.1), 282 (1.4), 99 (100); found m/z 344.2357, calcd for $C_{22}H_{32}O_3$ (M) 344.2352.

8α-(2-Acetoxyethyl)-2-(ethylenedioxy)-7-methylene-1α,4aβ,8aβ-trimethyl-1,2,3,4,4a,6,7,8,8a,9-decahydrophenanthrene (26). To a solution of alcohol 22 (5.2 g, 15.1 mmol) in dry pyridine (150 mL) was added acetic anhydride (50 mL, 530 mmol), and the solution was stirred at 0 °C for 3 h under N_2. After addition of methanol, removal of solvents afforded crude acetate 26 (5.2 g). Purification by silica gel (150 g) column chromatography (4% acetone in benzene) afforded pure acetate 26 (4.74 g; 81%) as an oil: IR (neat) 1740, 1670 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (3 H, d, J = 7 Hz), 1.11 (3 H, s), 1.27 (3 H, s), 2.03 (3 H, s), 3.7– 4.1 (6 H, m), 4.68 (1 H, s), 4.79 (1 H, s), 5.48 (2 H, m); MS m/z (%) 386 (M^+, 5), 326 (0.4), 99 (100); found m/z 386.2462, calcd for $C_{24}H_{34}O_4$ (M) 386.2457.

8α-(2-Acetoxyethyl)-2-(ethylenedioxy)-7-methylene-1α,4aβ,8aβ-trimethyl-1,2,3,4,4a,6,7,8,8a,9-decahydrophenanthren-6-one (27). Chromium(VI) oxide (26 g, 260 mmol) was gradually added into a mixture of dry CH_2Cl_2 (750 mL) and dry pyridine (75 mL) and was stirred for 1 h. A solution of acetate 26 (4.74 g, 12.3 mmol) in dry CH_2Cl_2 (300 mL) was added to the mixture and was stirred for 2 h. After addition of powdered $KHSO_4$ (10 g) and stirring, the reaction mixture was filtered through a Florisil column with ethyl acetate and was purified by silica gel (150 g) column chromatography (2–4% acetone in benzene) to afford enone 27 (3.50 g; 71%) as an oil: IR (neat) 1735, 1660, 1610, 1600 cm^{-1}; UV (EtOH) 256 nm (ϵ 10 000); ^1H NMR (90 MHz, $CDCl_3$) δ 1.03 (3 H, d, J = 7 Hz), 1.31 (3 H, s), 1.37 (3 H, s), 2.02 (3 H, s), 3.8–4.1 (6 H, m), 5.19 (1 H, s), 6.00 (1 H, s), 5.55 (1 H, dd, J = 6 and 1.5 Hz), 6.11 (1 H, s); MS m/z (%) 400 (M^+, 1.5), 356 (0.5), 99 (100); found m/z 400.2260, calcd for $C_{24}H_{32}O_5$ (M) 400.2250.

8α-(2-Acetoxyethyl)-2-(ethylenedioxy)-1α,4aβ,7α,8aβ-tetramethyl-1,2,3,4,4a,6,7,8,8a,9-decahydrophenanthren-6-one (28). A mixture of platinum oxide (500 mg, 2.2 mmol) and dry ethanol (50 mL) was stirred under a hydrogen atmosphere at atmospheric pressure and room temperature for 0.5 h. A solution of enone 27 (3.47 g, 8.67 mmol) in dry ethanol (150 mL) was added to the mixture and was stirred under the hydrogen atmosphere for 2 h. After the removal of catalyst by filtration followed by

(26) Ruest, L.; Blouin, G.; Deslongchamps, P. *Synth. Commun.* **1976**, *6*, 169.

evaporation, purification by silica gel (120 g) column chromatography (5% acetone in benzene) afforded ketone **28** (2.88 g; 83%) as an oil: IR (neat) 1740, 1670, 1600 cm^{-1}; UV (EtOH) 243 nm (ϵ 7300); ^1H NMR (90 MHz, $CDCl_3$) δ 1.04 (3 H, d, J = 7 Hz), 1.14 (3 H, d, J = 7 Hz), 1.36 (3 H, s), 1.44 (3 H, s), 2.03 (3 H, s), 2.78 (1 H, qd, J = 7 and 1.5 Hz), 2.96 (1 H, qd, J = 7 and 4 Hz), 3.7–4.3 (6 H, m), 5.53 (1 H, dd, J = 6 and 1.5 Hz), 5.95 (1 H, s); MS m/z (%) 402 (M^+, 3), 99 (100); found m/z 402.2401, calcd for $C_{24}H_{34}O_5$ (M) 402.2404.

2-(Ethylenedioxy)-8α-(2-hydroxyethyl)-1α,4aβ,7α,8aβ-tetramethyl-1,2,3,4,4a,6,7,8,8a,9-decahydrophenanthren-6-one (12). A solution of acetate **28** (2.88 g, 7.16 mmol) in methanol (400 mL) was added to a solution of KOH (8 g, 0.14 mol) in methanol (500 mL) and water (140 mL), and the solution was stirred for 0.5 h at room temperature under N_2. After removal of methanol followed by addition of water, the reaction mixture was extracted with ether three times and dried ($MgSO_4$). After evaporation, white crystalline alcohol **12** (2.33 g; 90%) was obtained: mp 174–175 °C; IR (KBr) 3450, 1670, 1660, 1600 cm^{-1}; UV (EtOH) 244 nm (ϵ 8000); ^1H NMR (90 MHz, $CDCl_3$) δ 1.03 (3 H, d, J = 7 Hz), 1.15 (3 H, d, J = 7 Hz), 1.36 (3 H, s), 1.44 (3 H, s), 2.96 (1 H, qd, J = 7 and 4 Hz), 3.50 (2 H, t, J = 7 Hz), 3.8–4.1 (4 H, m), 5.53 (1 H, br d, J = 6 Hz), 5.95 (1 H, s); MS m/s (%) 360 (M^+, 2), 99 (100). Anal. Found: C, 73.02; H, 8.92; m/z 360.2314. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; (M) 360.2301.

3-(Ethylenedioxy)picrasa-5,9(11)-dien-12-one (13). A solution of alcohol **12** (2.28 g, 6.33 mmol) in dry benzene (800 mL) was added to a mixture of lead tetraacetate (4.50 g, 10.1 mmol) and calcium carbonate (3.0 g, 30 mmol), and the mixture was refluxed under sun-lamp (250-W) irradiation for 16 h. Water was added, and the mixture was extracted with ether three times. After being washed with aqueous $NaHCO_3$ (twice) and brine (once), the ether solution was dried ($MgSO_4$). Removal of solvent and purification by silica gel (120 g) column chromatography (4–10% acetone in benzene) afforded the unreacted starting material **12** (0.76 g; 33%) and picrasane ether **13** (1.17 g; 52%) as crystals: mp 206–208 °C; IR (KBr) 1680, 1610 cm^{-1}; UV (EtOH) 241 nm (ϵ 8600); ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (3 H, d, J = 7 Hz), 1.09 (3 H, d, J = 7 Hz), 1.32 (3 H, s), 1.34 (3 H, s), 2.77 (1 H, q, J = 7 Hz, 4-H), 2.97 (1 H, qd, J = 7 and 4 Hz, 13-H), 3.40 (1 H, td, J = 12 and 3 Hz, 16β-H), 3.53 (1 H, d, J = 6 Hz, 7β-H), 3.80–4.05 (5 H, m, acetal-H_4 and 16α-H), 5.70 (1 H, dd, J = 6 and 1.5 Hz, 6-H), 6.07 (1 H, s, 11-H); MS m/z (%) 358 (M^+, 1.5), 314 (0.2), 99 (100). Anal. Found: C, 73.50; H, 8.51; m/z 358.2158. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; (M) 358.2145.

3-(Ethylenedioxy)picras-5-en-12-one (29). At −78 °C a solution of enone **13** (10.6 mg, 0.03 mmol) in THF (2 mL) was added to a blue mixture of lithium (50 mg, 7.2 mmol) and liquid ammonia (20 mL), and the mixture was refluxed at −33 °C for 0.5 h. Aqueous NH_4Cl was added at −78 °C quickly, and the system was warmed up to room temperature while removing ammonia as much as possible. After careful addition of 2 M HCl, the mixture was extracted with ether three times. The ether solution was washed with aqueous $NaHCO_3$ (three times) followed by saturated aqueous NaCl (twice), dried ($MgSO_4$), and evaporated. Preparative thin-layer chromatography on silica gel with ether–benzene (4:1) yielded saturated ketone **29** (6.5 mg; 61%) as white crystals: mp 183–186 °C; IR (KBr) 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 6.5 Hz, 13-Me), 1.01 (3 H, d, J = 6.5 Hz, 4-Me), 1.07 (3 H, s, 10-Me), 1.19 (3 H, s, 8-Me), 1.80 (1 H, dt, J = 13 and 5 Hz, 14β-H), 2.72 (1 H, q, J = 6.5 Hz, 4β-H), 2.97 (1 H, qd, J = 6.5 and 5 Hz, 13β-H), 3.35 (1 H, td, J = 12 and 2 Hz, 16β-H), 3.47 (1 H, d, J = 6 Hz, 7β-H), 3.75–3.91 (4 H, m, acetal-H_4), 4.01 (1 H, ddd, J = 11, 4, and 2 Hz, 16α-H), 5.55 (1 H, dd, J = 6 and 2 Hz, 6-H); MS m/z (%) 360 (M^+, 1), 345 (0.2), 316 (0.2), 99 (100); found m/z 360.2297, calcd for $C_{22}H_{32}O_4$ (M) 360.2299.

3-(Ethylenedioxy)picras-5-en-12β-ol (30). A solution of enone **13** (680 mg, 1.9 mmol) in dry THF (50 mL) was added to a blue mixture of lithium (460 mg, 66 mmol) and liquid ammonia (50 mL) at −78 °C, and the mixture was refluxed at −33 °C for 40 min. After dry ethanol (25 mL) was added at −78 °C and the mixture was again refluxed for 10 min, aqueous NH_4Cl (20 mL) was added at −78 °C quickly and the mixture was warmed to room temperature with removal of ammonia as much as possible. The mixture was neutralized on careful addition of 2 M HCl and was extracted with $CHCl_3$ (three times). The $CHCl_3$ solution was washed with aqueous $NaHCO_3$ (three times) followed by brine (once) and was dried ($MgSO_4$). After evaporation, column chromatography on silica gel (50 g) with benzene–ethyl acetate (1:3) afforded alcohol **30** (580 mg; 84%) as white crystals: mp 208–210 °C; IR (KBr) 3500 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.99 (3 H, s), 1.00 (6 H, d, J = 7 Hz, 4-Me and 13-Me), 1.04 (3 H, s), 2.71 (1 H, qd, J = 7 and 1.5 Hz, 4β-H), 3.1–3.7 (3 H, m, 7β-H, 12β-H, and 16β-H), 3.8–4.2 (5 H, m, acetal-H_4 and 16α-H), 5.50 (1 H, dd, J = 6 and 1.5 Hz, 6-H); MS m/z (%) 362 (M^+, 1.4), 347 (0.3), 99 (100). Anal. Found: C, 72.65; H, 9.53; m/z 362.2483. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45; (M) 362.2457.

12β-Hydroxypicras-4-en-3-one (31). Acetal **30** (470 mg, 1.29 mmol) was added to a mixture of THF (200 mL) and 3 M HCl (50 mL), and the whole was stirred at room temperature for 1 h and at 60 °C for 15 min. After addition of water (50 mL), the mixture was extracted with ether three times, dried ($MgSO_4$), and evaporated. Column chromatography on silica gel (50 g) with benzene–ethyl acetate (1:2) afforded enone **31** (370 mg; 90%) as white crystals: mp 208–210 °C; IR (KBr) 3450, 1660, 1600 cm^{-1}; UV (EtOH) 252 nm (ϵ 8300); ^1H NMR (90 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 7 Hz, 13-Me), 1.14 (3 H, s), 1.25 (3 H, s), 1.82 (3 H, s, 4-Me), 3.2–3.8 (3 H, m, 7β-H, 12β-H, and 16β-H), 4.02 (1 H, dd, J = 11 and 3 Hz, 16α-H); MS m/z (%) 318 (M^+, 100), 303 (31), 300 (31), 285 (24). Anal. Found: C, 75.29; H, 9.28; m/z 318.2180. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50; (M) 318.2193.

12β-(1-Ethoxyethoxy)picras-4-en-3-one (32). Pyridinium *p*-toluenesulfonate (30 mg, 0.12 mmol) and ethyl vinyl ether (14 mL, 0.15 mol) were added to a solution of alcohol **31** (338 mg, 1.06 mmol) in dry CH_2Cl_2 (200 mL), and the mixture was stirred at room temperature for 2.5 h. After addition of ether (200 mL), the mixture was washed with brine three times and was dried ($MgSO_4$). After removal of solvents, ether **32** (410 mg; 99%) was obtained as an oil: IR (neat) 1670, 1615 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 and 0.97 (each 1.5 H, d, J = 7 Hz, 13-Me), 1.12 (3 H, s), 1.22 (3 H, s), 1.23 (3 H, t, J = 6 Hz, OCH_2CH_3), 1.31 (3 H, d, J = 5 Hz, 1′-Me), 1.79 (3 H, s, 4-Me), 3.21 (1 H, td, J = 11 and 5 Hz, 16β-H), 3.32 (1 H, br s, 7β-H), 4.00 (1 H, dd, J = 11 and 4 Hz, 16α-H), 4.63 and 4.80 (each 0.5 H, q, J = 5 Hz, 1′-H); MS m/z (%) 390 (M^+, 28), 318 (71), 301 (92), 300 (100); found m/z 390.2772, calcd for $C_{24}H_{38}O_4$ (M) 390.2771.

12β-(1-Ethoxyethoxy)picrasan-3-one (33) and 12β-(1-Ethoxyethoxy)picrasan-3β-ol (34). A solution of enone **32** (128 mg, 0.328 mmol) in dry THF (50 mL) was added to a blue mixture of lithium (300 mg, 43 mmol) and liquid ammonia (100 mL) at −78 °C, and the mixture was refluxed at −33 °C for 40 min. After aqueous NH_4Cl was added at −78 °C quickly, the mixture was warmed to room temperature with removal of ammonia as much as possible, extracted with ether five times, and dried ($MgSO_4$). Column chromatography on silica gel (10 g) with 4–10% acetone in benzene afforded ketone **33** (69 mg; 54%) and alcohol **34** (31 mg; 24%). Ketone **33**: oil; IR (neat) 1710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.91 and 0.95 (each 1.5 H, d, J = 7 Hz, 13-Me), 0.97 (3 H, d, J = 7 Hz, 4-Me), 1.01 (3 H, s), 1.11 (3 H, s), 1.18 (3 H, t, J = 6 Hz, OCH_2CH_3), 1.30 (3 H, d, J = 5 Hz, 1′-Me), 3.19 (1 H, t, J = 3 Hz, 7β-H), 4.03 (1 H, dd, J = 11 and 4 Hz, 16α-H), 4.64 and 4.78 (each 0.5 H, q, J = 5 Hz, 1′-H); MS m/z (%) 392 (M^+, 17), 320 (19), 303 (100), 302 (35); found m/z 392.2925, calcd for $C_{24}H_{40}O_4$ (M) 392.2925. Alcohol **34**: oil; IR (neat) 3700–3100 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.79 (3 H, s), 0.89 (3 H, d, J = 7 Hz), 0.93 (3 H, d, J = 7 Hz), 1.05 (3 H, s), 1.18 (3 H, t, J = 6 Hz, OCH_2CH_3), 1.30 (3 H, d, J = 5 Hz, 1′-Me), 4.03 (1 H, dd, J = 11 and 3 Hz, 16α-H), 4.61 and 4.77 (each 0.5 H, q, J = 5 Hz, 1′-H); MS m/z (%) 394 (M^+, 0.6), 379 (1.3), 348 (2.4), 322 (5), 305 (100), 304 (57); found m/z 394.3114, calcd for $C_{24}H_{42}O_4$ (M) 394.3083.

Oxidation of Alcohol 34 into Ketone 33. Chromium(VI) oxide (70 mg, 0.7 mmol) was added to a mixture of dry CH_2Cl_2 (3 mL) and dry pyridine (0.1 mL) and was stirred for several minutes. A solution of alcohol **34** (31 mg, 0.078 mmol) in dry CH_2Cl_2 (5 mL) was added to the mixture, and the whole was stirred for 3 h. After addition of $NaHSO_4$, the mixture was passed through a Florisil column with ethyl acetate. After evaporation, column chromatography on silica gel (5 g) with 4% acetone in benzene afforded ketone **33** (23 mg; 75%) as an oil, which was identical with the one mentioned above.

12β-Hydroxypicrasan-3-one (14). To a solution of ether **33** (66.5 mg, 0.17 mmol) in THF (120 mL) was added 0.5 M HCl (24

mL) at 0 °C, and the mixture was stirred at room temperature for 3.5 h. After careful addition of aqueous $NaHCO_3$, the mixture was extracted with ether three times and was dried ($MgSO_4$). After evaporation, silica gel (5 g) column chromatography (10% acetone in benzene) afforded keto alcohol **14** (52 mg; 96%) as white crystals: mp 158–160 °C; IR (KBr) 3450, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (6 H, d, J = 7 Hz, 4-Me and 13-Me), 1.00 (3 H, s), 1.10 (3 H, s), 2.40 (1 H, dq, J = 11 and 7 Hz, 4β-H), 3.22 (1 H, br s, $W_{1/2}$ = 8 Hz, 7β-H), 3.35 (1 H, td, J = 10 and 1.5 Hz, 16β-H), 3.41 (1 H, td, J = 10 and 4 Hz, 12α-H), 4.01 (1 H, dd, J = 10 and 4 Hz, 16α-H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 11.67 (q), 13.46 (q), 15.28 (q), 22.48 (q), 22.48 (t), 28.12 (t), 31.39 (t), 36.54 (s), 37.11 (t), 37.11 (d), 37.30 (s), 39.30 (t), 41.98 (d), 44.15 (d), 45.23 (d), 50.71 (d), 68.50 (t), 72.89 (d), 80.12 (d), 213.06 (s); MS m/z (%) 320 (M^+, 100), 305 (22), 302 (33), 287 (20). Anal. Found: C, 74.78; H, 10.14; m/z 320.2386. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; (M) 320.2351.

12β-Hydroxypicras-1-en-3-one (38). Phenylselenenyl chloride (184 mg, 0.96 mmol) and p-toluenesulfonic acid (10 mg, 0.053 mmol) were added to a solution of ketone **14** (168 mg, 0.525 mmol) in dry ethyl acetate (100 mL) at 0 °C, and the mixture was stirred at room temperature for 5 h. Aqueous $NaHCO_3$ was added at 0 °C, and the organic layer was washed with the same aqueous solution. Pyridine (20 mL) and 80% m-chloroperbenzoic acid (350 mg, 1.62 mmol) were added to the separated organic layer at 0 °C, and the mixture was stirred at room temperature for 1 h. After being washed with aqueous $NaHCO_3$ (three times) followed by brine (twice), the organic layer was dried ($MgSO_4$). Evaporation followed by purification by silica gel (15 g) column chromatography (5–15% acetone in benzene) afforded enone **38** (117 mg; 70%) as an oil: IR (neat) 3450, 1680 cm^{-1}; UV (EtOH) 228 nm (ϵ 7300); ^1H NMR (90 MHz, $CDCl_3$) δ 0.98 (3 H, d, J = 7 Hz), 1.06 (3 H, s), 1.10 (3 H, d, J = 7 Hz), 1.14 (3 H, s), 3.23 (1 H, t, J = 3 Hz, 7β-H), 4.02 (1 H, dd, J = 10 and 4 Hz, 16α-H), 5.77 (1 H, d, J = 10 Hz, 2-H), 7.13 (1 H, d, J = 10 Hz, 1-H); MS m/z (%) 318 (M^+, 82), 300 (100), 285 (17), 255 (24); found m/z 318.2211, calcd for $C_{20}H_{30}O_3$ (M) 318.2195.

12β-(1-Ethoxyethoxy)-1α,2α-epoxypicrasan-3-one (41). Pyridinium p-toluenesulfonate (50 mg, 0.2 mmol) and ethyl vinyl ether (4 mL, 42 mmol) were added to a solution of alcohol **38** (116 mg, 0.365 mmol) in dry CH_2Cl_2 (50 mL), and the mixture was stirred at room temperature for 2 h. After addition of ether, the organic layer was washed with brine twice and dried ($MgSO_4$). Evaporation followed by silica gel (5 g) column chromatography (10% acetone in benzene) afforded 12β-(1-ethoxyethoxy)picras-1-en-3-one (123 mg; 86%) as an oil: IR (neat) 1680 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.92 and 0.96 (each 1.5 H, d, J = 7 Hz, 13-Me), 1.05 (3 H, s), 1.09 (3 H, d, J = 6 Hz, 4-Me), 1.13 (3 H, s), 1.24 and 1.31 (each 0.5 H, d, J = 5 Hz, 1'-H), 1.30 (3 H, t, J = 6 Hz, OCH_2CH_3), 3.24 (1 H, t, J = 3 Hz, 7β-H), 4.04 (1 H, dd, J = 10 and 4 Hz, 16α-H), and 4.67 and 4.86 (each 0.5 H, q, J = 5 Hz, 1'-H); MS m/z (%) 390 (M^+, 20), 375 (8), 318 (61), 301 (100), 300 (69); found m/z 390.2759, calcd for $C_{24}H_{38}O_4$ (M) 390.2769. To a solution of the enone (122 mg, 0.312 mmol) in THF (50 mL) were added 2 M aqueous NaOH and a mixture of 30% H_2O_2 (2.5 mL) and methanol (4 mL) at 0 °C. The mixture was stirred at room temperature for 4 h. At 0 °C aqueous $NaHCO_3$ and aqueous $NaHSO_3$ were added successively. The mixture was extracted with ether (three times), washed with aqueous $NaHCO_3$ (three times) and brine (twice), and dried ($MgSO_4$). After evaporation, column chromatography on silica gel (5 g) with 7% acetone in benzene afforded an epoxide **41** (109 mg; 86%) as an oil: IR (neat) 1710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.89 (3 H, s), 0.96 and 1.00 (each 1.5H, d, J = 7 HZ, 13-Me), 1.09 (3 H, s), 1.11 (3 H, d, J = 6 Hz, 4-Me), 1.18 (3 H, t, J = 6 Hz, OCH_2CH_3), 1.31 (3 H, d, J = 5 Hz, 1'-Me), 4.06 (1 H, dd, J = 10 and 4 Hz, 16α-H), 4.64 and 4.80 (each 0.5 H, q, J = 5 Hz, 1'-H); MS m/z (%) 406 (M^+, 0.3), 391 (7), 317 (100), 316 (24), 301 (35); found m/z 406.2709, calcd for $C_{24}H_{38}O_5$ (M) 406.2717.

12β-(1-Ethoxyethoxy)picrasane-1α,3β-diol (42). To a suspension of $LiAlH_4$ (160 mg, 4.2 mmol) in dry ether (10 mL) was added a mixture of *tert*-butyl alcohol (1.2 mL) and dry ether (10 mL) at 0 °C, and the mixture was stirred for 30 min at the same temperature. A solution of epoxy ketone **41** (296 mg, 0.728 mmol) in dry ether (25 mL) was added to the mixture, and the whole was stirred at 0 °C for 1 h and at room temperature for 30 min. After addition of cracked ice, the mixture was extracted with ether three times, dried ($MgSO_4$), and evaporated. A solution of the oily product in dry THF (30 mL) was added $LiAlH_4$ (100 mg, 2.6 mmol), and the mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. After addition of water, the mixture was extracted with ether once and ethyl acetate twice, and the combined organic layer was dried ($MgSO_4$). Evaporation followed by silica gel (20 g) column chromatography (20–40% acetone in benzene) afforded 1α,3β-diol **42** (255 mg; 85%) as a more polar product and a corresponding 1α,3α-diol (19 mg; 7%) as a less polar product. The major product **42** was an oil: IR 3470 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.86 (3 H, s), 0.90 and 1.02 (each 1.5 H, d, J = 6 Hz, 13-Me), 0.96 (3 H, d, J = 6 Hz, 4-Me), 1.09 (3 H, s), 1.23 (3 H, d, J = 5 Hz, 1'-H), 1.26 (3 H, t, OCH_2CH_3), 3.0–3.9 (7 H, m, 1β-H, 3α-H, 7β-H, 12α-H, 16β-H, and OCH_2CH_3), 4.06 (1 H, dd, J = 10 and 4 Hz, 16α-H), 4.69 and 4.85 (each 0.5 H, q, J = 5 Hz, 1'-H); MS m/z (%) 364((M – EtOH)$^+$, 15), 321 (84), 320 (100), 303 (83), 302 (75), 285 (60); found m/z 364.2575, calcd for $C_{24}H_{42}O_5$ (M – EtOH) 364.2611. 12β-(1-Ethoxyethoxy)picrasane-1α,3α-diol was an oil: IR (neat) 3700–3100 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.75 (3 H, s), 0.96 and 1.02 (each 1.5 H, d, J = 6 Hz, 13-Me), 0.96 (3 H, d, J = 7 Hz, 4-Me), 1.08 (3 H, s), 1.20 (3 H, d, J = 5 Hz, 1'-Me), 1.23 (3 H, t, J = 6 Hz, OCH_2CH_3), 2.90 (1 H, br s, intramolecular hydrogen-bonded OH), 3.0–3.9 (7 H, m, 1β-H, 3β-H, 7β-H, 12α-H, 16β-H, and OCH_2CH_3), 4.08 (1 H, dd, J = 10 and 4 Hz, 16α-H), 4.65 and 4.79 (each 0.5 H, q, J = 5 Hz, 1'-H); MS m/z (%) 364 (2), 349 (2), 346 (2), 320 (35), 302 (38), 285 (100).

12β-Hydroxypicras-2-en-1-one (44). To a solution of diol **42** (138 mg, 0.379 mmol) in dry pyridine (20 mL) was added p-toluenesulfonyl chloride (320 mg, 1.68 mmol), and the mixture was stirred at 0 °C under N_2 for 2 days. After addition of water followed by 2 M HCl for a very weakly acidified condition, the mixture was quickly extracted with ether three times. The ether layer was washed with aqueous $NaHCO_3$ (three times) and brine (once) and was dried ($MgSO_4$). Evaporation afforded crude oily monotosylate **43** (190 mg; 97%): 12β-(1-ethoxyethoxy)-3β-(tosyloxy)picrasan-1α-ol: ^1H NMR (90 MHz, $CDCl_3$) δ 2.40 (3 H, br s, aromatic Me), 4.3–5.0 (2 H, m, 3α-H and 1'-H), 7.30 (2 H, d, J = 8 Hz), 7.75 (2 H, d, J = 8 Hz).

Chromium(VI) oxide (200 mg, 2 mmol) was added to a stirring mixture of dry CH_2Cl_2 (5 mL) and dry pyridine (1 mL), and the mixture was stirred at room temperature for 30 min. The crude tosylate **43** (190 mg, 0.37 mmol) was added to the mixture, and the whole was stirred at room temperature for 1 h. Addition of powdered $KHSO_4$ followed by filtration through Florisil with ethyl acetate and evaporation afforded crude oily ketone (183 mg; 96%) 12β-(1-ethoxyethoxy)-3β-(tosyloxy)picrasan-1-one: ^1H NMR (90 MHz, $CDCl_3$) δ 2.40 (3 H, br s, aromatic Me), 4.65 (1 H, q, J = 5 Hz, 1'-H), 7.27 (2 H, d, J = 8 Hz), 7.73 (2 H, d, J = 8 Hz). To a solution of the crude tosyloxy ketone (183 mg, 0.35 mmol) in dry THF (20 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1 mL, 6.7 mmol), and the mixture was refluxed for 2 h. After addition of aqueous NH_4Cl, the mixture was extracted with ether three times and was dried ($MgSO_4$). Evaporation followed by silica gel (15 g) column chromatography with 10% acetone in benzene afforded enone (118 mg; 90% from **42**) 12β-(1-ethoxyethoxy)picras-2-en-1-one: oil; IR (neat) 1685, 1110 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.92 and 0.97 (each 1.5 H, d, J = 7 Hz, 13-Me), 1.08 (3 H, d, J = 7 Hz, 4-Me), 1.13 (3 H, s), 1.15 (3 H, s), 3.16 (1 H, t, J = 3 Hz, 7β-H), 3.35 (1 H, td, J = 11 and 2 Hz, 16β-H), 4.02 (1 H, dd, J = 11 and 4 Hz, 16α-H), 4.69 and 4.81 (each 0.5 H, q, J = 5 Hz, 1'-H), 5.68 (1 H, dd, J = 10 and 3 Hz, 2-H), 6.44 (1 H, br d, J = 10 Hz, 3-H); MS m/z (%) 344 ((M – EtOH)$^+$, 2.5), 318 (14), 300 (100), 285 (27), 282 (53).

To a solution of the 12β-(1-ethoxyethoxy)picras-2-en-1-one (118 mg, 0.303 mmol) in dry ethyl acetate (20 mL) was added p-toluenesulfonic acid (30 mg, 0.16 mmol), and the mixture was stirred at room temperature for 1 h. After washing with aqueous solution of $NaHCO_3$ (three times) and saturated aqueous NaCl (twice) followed by drying ($MgSO_4$), evaporation followed by silica gel (10 g) column chromatography (15% acetone in benzene) afforded deprotected enone **44** (96 mg; 100%) as an oil: IR (neat) 3400, 1675, 1625 cm^{-1}; UV (EtOH) 225 nm (ϵ 6800); ^1H NMR (90 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 1.12 (3 H, s), 1.14 (3 H, s), 3.16 (1 H, t, J = 3 Hz, 7β-H), 3.34 (1

H, td, J = 11, and 2 Hz, 16β-H), 3.60 (1 H, td, J = 10 and 4 Hz, 12α-H), 4.01 (1 H, dd, J = 11 and 4 Hz, 16α-H), 5.66 (1 H, dd, J = 10 and 3 Hz, 2-H), 6.43 (1 H, dd, J = 10 and 2 Hz, 3-H); MS m/z (%) 318 (M^+, 100), 303 (1), 300 (2), 285 (2); found m/z 318.2210, calcd for $C_{20}H_{30}O_3$ (M) 318.2195.

12β-Hydroxypicrasan-1-one (45). After a mixture of 10% palladium–charcoal (20 mg) in absolute ethanol (2 mL) was stirred for 30 min under a hydrogen atmosphere at atmospheric pressure and room temperature, a solution of enone **44** (90 mg, 0.28 mmol) in absolute ethanol (8 mL) was added, and the whole mixture was stirred at room temperature for 1.5 h under the hydrogen atmosphere. After filtration for removal of catalyst, evaporation followed by silica gel (8 g) column chromatography (25% acetone in benzene) afforded hydroxy ketone **45** (90 mg; 100%) as an oil: IR (neat) 3450, 1700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.86 (3 H, d, J = 6 Hz), 0.96 (3 H, d, J = 7 Hz), 1.07 (3 H, s), 1.19 (3 H, s), 3.16 (1 H, t, J = 3 Hz, 7β-H), 3.33 (1 H, td, J = 11 and 2 Hz, 16β-H), 3.61 (1 H, td, J = 10 and 4 Hz, 12α-H), 4.03 (1 H, dd, J = 11 and 4 Hz, 16α-H); MS m/z (%) 320 (M^+, 4), 302 (100), 287 (31), 284 (39); found m/z 320.2375, calcd for $C_{20}H_{32}O_3$ (M) 320.2350.

Picrasane-1,12-dione (15). Chromium(VI) oxide (200 mg, 2 mmol) was added to a stirring mixture of dry CH_2Cl_2 (5 mL) and dry pyridine (1 mL), and the mixture was stirred at room temperature for 30 min. A solution of hydroxy ketone **45** (90 mg, 0.28 mmol) in dry CH_2Cl_2 (8 mL) was added to the mixture, and the whole was stirred at room temperature for 1 h. Addition of powdered $KHSO_4$ followed by filtration through Florisil with ethyl acetate, evaporation, and silica gel (8 g) column chromatography (15% acetone in benzene) afforded diketone **15** (89 mg; 99%) as white crystals: mp 206–207.5 °C (from benzene); IR (KBr) 1700, 1105 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.87 (3 H, d, J = 6 Hz), 0.94 (3 H, d, J = 7 Hz), 1.22 (3 H, s), 1.29 (3 H, s), 3.27 (1 H, t, J = 3 Hz, 7β-H), 3.38 (1 H, td, J = 12 and 2 Hz, 16β-H), 4.02 (1 H, dd, J = 12 and 3 Hz, 16α-H); MS m/z (%) 318 (M^+, 47), 300 (100), 285 (20), 219 (90); found m/z 318.2177, calcd for $C_{20}H_{30}O_3$ (M) 318.2193.

2α,11α-Dihydroxypicrasane-1,12-dione (16). A solution of diketone **15** (21 mg, 0.066 mmol) in dry THF (5 mL) was added at −78 °C to a THF solution of 2 molar equiv of LDA prepared beforehand under N_2, and the mixture was stirred for 1 h at the same temperature followed by the addition of trimethylchlorosilane (0.1 mL, 0.8 mmol). After addition of saturated aqueous NaCl, the reaction mixture was extracted with ether three times. Dryness ($MgSO_4$) followed by evaporation afforded 1,12-bis(trimethylsiloxy)picrasa-1,11-diene (**46**) (30.5 mg; 100%): ^1H NMR (90 MHz, $CDCl_3$) δ 0.27 (18 H, s), 0.90 (3 H, d, J = 7 Hz), 0.98 (3 H, d, J = 7 Hz), 1.02 (3 H, s), 1.12 (3 H, s), 2.80 (1 H, br s, 9-H), 3.23 (1 H, br s, 7-H), 3.47 (1 H, m, 16β-H), 4.08 (1 H, m, 16α-H), 4.47 (1 H, dd, J = 5 and 2 Hz, 2-H), 4.70 (1 H, br s, 11-H). Without further purification, the silyl enol–ether **46** (30.5 mg, 0.066 mmol) was dissolved to dry CH_2Cl_2 (9 mL). K_2CO_3 (60 mg) followed by 80% m-chloroperbenzoic acid (27 mg, 0.13 mmol) was added to the solution, and the whole mixture was stirred at 0 °C for 26 h. After addition of saturated aqueous $NaHCO_3$, the reaction mixture was extracted with CH_2Cl_2 (four times) and the organic layer was dried ($MgSO_4$). The oily substance obtained by evaporation was dissolved to THF (9 mL) followed by addition of 2 M HCl, and the mixture was stirred at room temperature for 1 h followed by evaporation to remove THF, addition of saturated aqueous NaCl, and extraction with $CHCl_3$ (three times). Drying ($MgSO_4$) followed by evaporation of solvent afforded an oily substance. Purification by silica gel (8 g) column chromatography (5–10% of acetone in benzene) afforded dihydroxy diketone **16** (15 mg; 65%) as white crystals: mp 209–209.5 °C (from benzene); IR (KBr) 3520, 3475, 1720, 1700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (3 H, d, J = 6 Hz), 1.03 (3 H, d, J = 6.5 Hz), 1.37 (3 H, s), 1.43 (3 H, s), 2.99 (1 H, d, J = 12.5 Hz, 9-H), 3.24 (1 H, t, J = 3 Hz, 7-H), 3.38 (1 H, m, 16β-H), 4.02 (1 H, m, 16α-H), 4.30 (1 H, d, J = 12.5 Hz, 11-H), 4.70 (1 H, m, 2-H); MS m/z (%) 350 (M^+, 43), 332 (75), 314 (17), 304 (37), 260 (100); found m/z 350.2139, calcd for $C_{20}H_{30}O_5$ (M) 350.2093.

2α,11α-Diacetoxypicrasane-1,12-dione (47). To a solution of diol **16** (8.5 mg, 0.024 mmol) in dry pyridine (4 mL) was added acetic anhydride (2 mL, 21 mmol), and the mixture was stirred at room temperature for 5 days under N_2. After saturated aqueous $NaHCO_3$ was added, the mixture was extracted with ether three times and was dried ($MgSO_4$). After evaporation, the crude oil was purified by silica gel (2.5 g) column chromatography (10% acetone in benzene) to afford diacetate **47** (9.5 mg; 90%) as a white solid: IR 1740 (sh), 1730, 1720 (sh) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.91 (3 H, d, J = 7 Hz), 0.99 (3 H, d, J = 7 Hz), 1.32 (3 H, s), 1.40 (3 H, s), 2.11 (6 H, s), 3.25 (1 H, br s, 7-H), 3.32 (1 H, d, J = 12.5 Hz, 9-H), 3.40 (1 H, m, 16β-H), 4.00 (1 H, m, 16α-H), 5.22 (1 H, d, J = 13 Hz, 11-H), 5.55 (1 H, dd, J = 11 and 8 Hz, 2-H); MS m/z (%) 434 (M^+, 1.2), 392 (6), 374 (100), 314 (27), 260 (51); found m/z 374.2092, calcd for $C_{22}H_{30}O_5$ ($M - CH_3CO_2H$) 374.2092.

2α,11α-Diacetoxypicrasane-1,12,16-trione ((±)-Amarolide Diacetate (48)). To a solution containing RuO_2 (15.5 mg, 0.116 mmol) in CCl_4 (2 mL) cooled to 0–5 °C was added to a solution of $NaIO_4$ (40 mg, 0.19 mmol) in H_2O (2 mL). After vigorous stirring of the two layers was continued for 30 min at 0 °C, the CCl_4 layer containing RuO_4 was separated and filtered. This CCl_4 solution of RuO_4 was added to a solution of diacetate **47** (8.0 mg, 0.021 mmol) in CCl_4 (1 mL), and the mixture was stirred at room temperature for 12 h. Addition of a drop of 2-propanol followed by filtration of RuO_2 and evaporation afforded a crude oil. Purification by silica gel (2.5 g) column chromatography (10% acetone in benzene) afforded (±)-amarolide diacetate (**48**; 2.2 mg; 27%) as white crystals together with a compound (2.0 mg) that might possess a hydroxyl group at C-7 like **49**. (±)-Amarolide diacetate (**48**): mp 251–252 °C; IR (KBr) 1740 (sh), 1730, 1725 (sh) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3 H, d, J = 7 Hz), 1.04 (3 H, d, J = 7.5 Hz), 1.39 (3 H, s), 1.57 (3 H, s), 2.12 (6 H, s), 2.99 (1 H, d, J = 14 Hz, 9-H), 4.31 (1 H, dd, J = 3.3 Hz, 7-H), 5.30 (1 H, d, J = 14 Hz, 11-H), 5.56 (1 H, dd, J = 12 and 8 Hz, 2-H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 10.4, 12.5, 18.5, 20.4, 20.5, 21.9, 26.5, 28.5, 29.0, 35.5, 36.3, 42.2, 42.7, 46.7, 47.6, 50.1, 72.3, 74.5, 81.7, 168.3, 169.8, 171.0, 201.9, 205.1; MS m/z (%) 448 (M^+, 4) 406 (7), 392 (27), 388 (62), 350 (60), 290 (97), 274 (100); found m/z 448.2143, calcd for $C_{24}H_{32}O_8$ (M) 448.2098.

(±)-Amarolide (1). To a solution of amarolide diacetate (**48**; 1.7 mg, 0.0038 mmol) in THF (1 mL) was added 3 M H_2SO_4 (1 mL), and the mixture was refluxed for 5 h. After evaporation for the removal of THF, the mixture was extracted with CH_2Cl_2 (four times) and dried ($MgSO_4$). Evaporation afforded crude crystals, which were purified by silica gel (2.5 g) column chromatography (30% acetone in benzene) to afford (±)-amarolide (1; 1.2 mg; 87%) as white crystals: mp 218–220 °C; IR (KBr) 3550, 1730, 1720, 1650, 1635 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7.5 Hz), 1.49 (3 H, s), 1.52 (3 H, s), 2.59 (1 H, d, J = 10 Hz, 11-OH), 2.62 (1 H, d, J = 12.5 Hz, 9-H), 3.05 (1 H, m, 13-H), 3.43 (1 H, d, J = 6 Hz, 2-OH), 4.29 (1 H, dd, J = 3.5 and 2.5 Hz, 7-H), 4.38 (1 H, dd, J = 12.5 and 10 Hz, 11-H), 4.77 (1 H, ddd, J = 11.5, 7.5 and 6 Hz, 2-H); MS m/z (%) 364 (M^+, 30), 346 (20), 318 (100); found m/z 364.1850, calcd for $C_{20}H_{28}O_6$ (M) 364.1885.

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Supplementary Material Available: ^{13}C NMR spectra for compounds **14** and **48** and ^1H NMR spectra for compounds **1**, **10–20**, **22**, **26–34**, **38**, **41**, **42**, **44**, **45**, **47**, **48**, and several other important compounds (37 pages). Ordering information is given on any current masthead page.