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Approach to the Synthesis of Antitumor Quassinoids from Labdane Diterpenes: An Efficient Synthesis of a Picrasane-Related Intermediate

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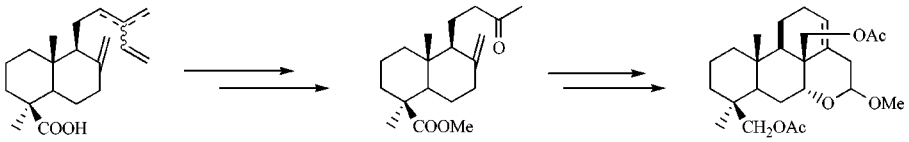
ABSTRACT



5a-c 9 24

The tetracyclic ketal 24, a suitable intermediate for the synthesis of antitumor pentacyclic quassinoids, has been efficiently prepared from communic acids (5a–c), via methyl ketone 9. The synthetic sequence from 9 to 24 consists of 15 steps in 12% overall yield.

Quassinoids are terpenoids, mainly found in Simaroubaceae species,[1] which exhibit a wide range of potent biological activities.[2] Among quassinoids, pentacyclic derivatives having picrasane skeleton are the most relevant because of their antitumor activity. Representative quassinoids of this type include bruceantine (**1**), a potent antileukemic agent,[3] simalikalactone D (**2**), an antimalarial compound 50 times more potent than quinine,[4] which shows potent in vivo activity against lymphocytic leukemia P-388 in mice,[5] and cedronolactone (**3**), which has a significant in vitro cytotoxicity against P-388 cells.[6] Despite the large number of studies on the synthesis of this class of compounds, only a few complete syntheses, involving low-yield, long sequences, have been reported.[7]

In continuation of our research into the synthesis of natural bioactive compounds based on enantiopure synthons obtained from natural sources,[8] we are developing a route to this type

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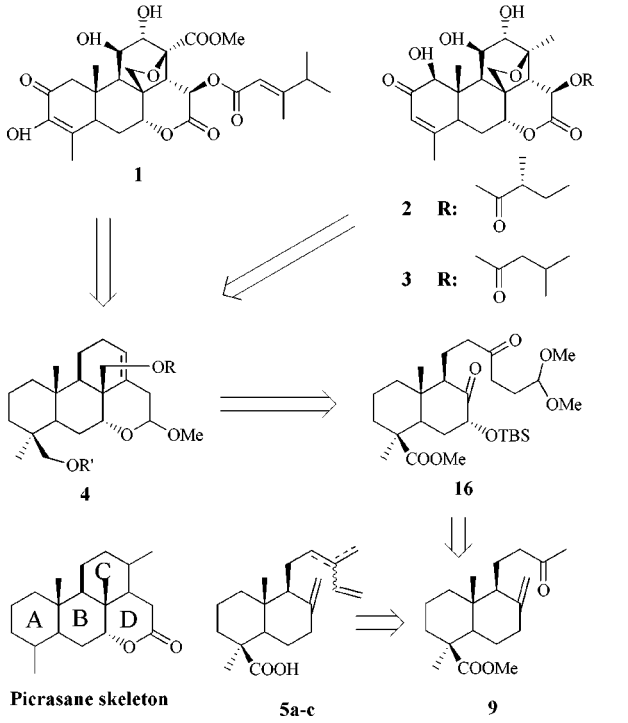
Scheme 1



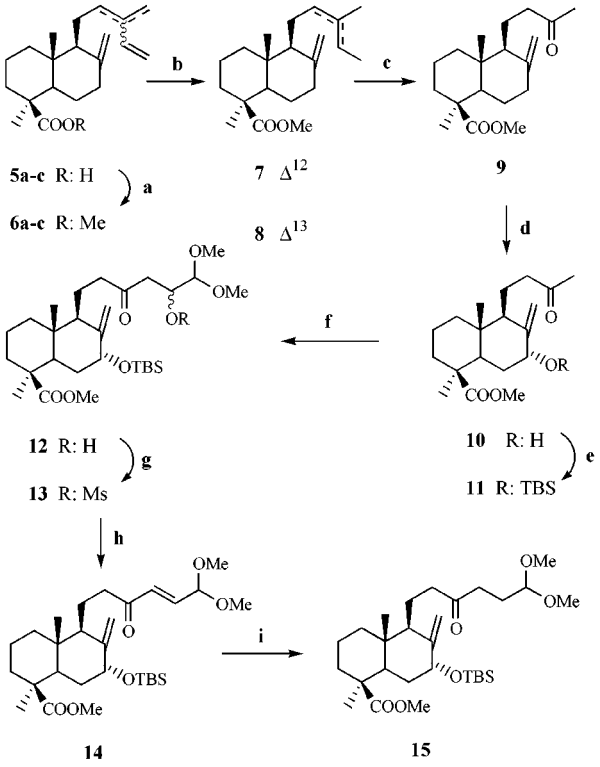
of quassinoid starting from communic acids (**5a**−**c**), the main diterpene constituents from Cupresaceae species, such as *Juniperus communis*.[9]

Acids **5a**−**c** contain the *trans*-decalin moiety that characterizes the A/B ring system of quassinoids, featuring both the absolute and the relative stereochemistry of carbons C-8, C-9, and C-10. Moreover, the carboxylic group on C-5 should allow the functionalization of the A ring, via degradation to the corresponding olefin, and the C8−C12 double bond would allow the oxygenated function to be introduced on C-7. The labdane side chain could be transformed into the C ring and enable the δ-lactone ring to be elaborated.

The retrosynthetic scheme (Scheme 1) involves three key intermediates, **4**, **16**, and **9**. Compound **4** has an acetal group that could be converted into the δ-lactone D-ring. The diosphenol or 1-hydroxy-3-en-2-one groups in the A ring of quassinoids could be obtained from the hydroxymethyl group on the C-4 in the intermediate **4**, via thermal rearrangement of the ozonide derived from the related aldehyde[10] or through the Baeyer−Villiger oxidation of this aldehyde.[11] Moreover, functionalization in the C-ring could easily be achieved by means of the C13−C14 double bond. The hydroxymethyl group in C-8 should enable the E bridged ether ring to be elaborated. Acetal **4** could be prepared by stereoselective hydrocyanation of the enone obtained after aldol condensation of **16**. The last compound could result from side chain lengthening by conventional methods and allylic oxidation on C-7 in **9**.

In this sequence the ready availability of large amounts of methyl ketone **9**[12] becomes very important The obtention of this compound from *Juniperus communis* berry extracts has recently been considerably improved (Scheme 2). Esterification of the acid fraction obtained from the hexane extract of dry plant material produced a mixture of methyl esters, containing **6a**−**c** as the main components.[13] When

Scheme 2



a. CH_2N_2, Et_2O, 0ºC; **b.** Na, t-BuOH, 60ºC, 18h (85%); **c.** OsO_4 0.2%, $NaIO_4$, t-BuOH-H_2O, rt, 5 day; Jones, acetone, rt; Et_2O / ac. Na_2CO_3; **d.** SeO_2, EtOH,60ºC, 12h (66%); **e**. TBSCl, imidazole, DMF, rt, 14h (94%); **f.** LDA, -78ºC, glyoxaldimethylacetal, THF, 30 min (95%); **g.** MsCl, Py, rt, 2.5h (94%); **h.** DBU, benzene, rt, 3h (92%); **i.** Raney Ni, THF, rt, 30 min (94%)

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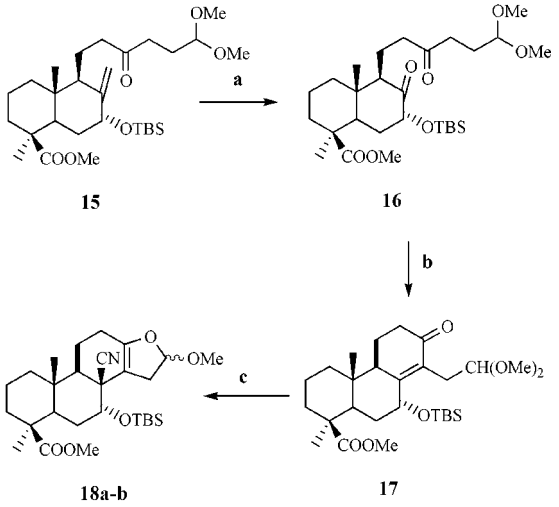
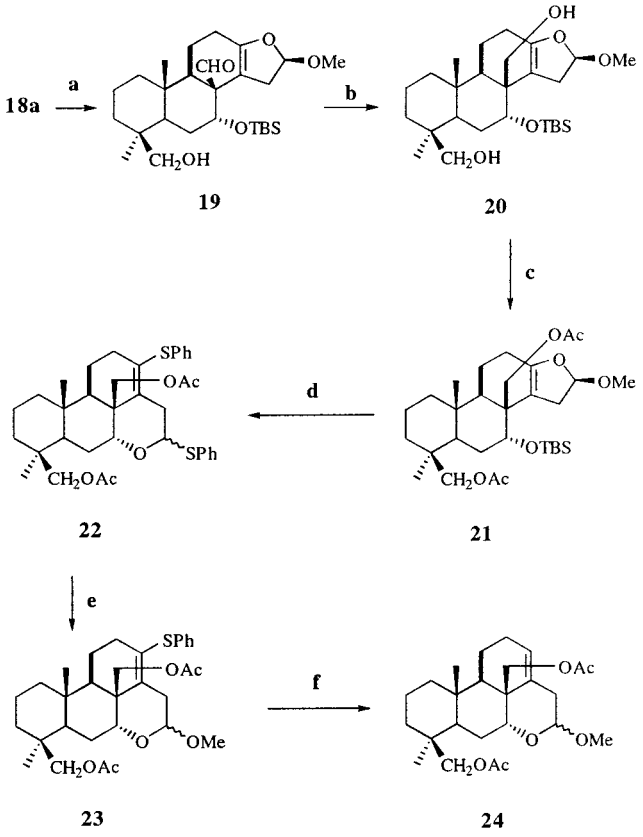
Scheme 3



a. O_3, CH_2Cl_2, -78°C, 15 min; Ph_3P, rt, 4h (91%); **b.** MeONa/MeOH, reflux, 11h (91%); **c.** KCN, Et_2AlCN, 18-crown-6 ether, toluene, 0°C--rt, 20h (87%)

Scheme 4



a. DIBAL, THF, rt, 3.5h; **b.** $NaBH_4$, EtOH, rt, 45 min (93%); **c.** Ac_2O, Py, rt, 4h (95%); **d.** PhSH, $BF_3.Et_2O$, CH_2Cl_2, rt, 5h (85%); **e.** $HgCl_2$, HgO, CH_3CN-MeOH, rt, 14h (82%); **f.** $NaBH_4$, $NiCl_2$, THF, reflux, 12h (63%)

this mixture was heated at 60 °C with sodium in *tert*-butanol, crude product consisted mainly of compounds **7** and **8** (ratio 2:8), resulting from 1,2- and 1,4-reduction, respectively. By oxidation of the reduction mixture with osmium tetroxide and sodium metaperiodate and then with Jones' reagent, a crude product with a ^{1}H NMR spectrum that revealed the presence of more than 95% of methyl ketone **9** was obtained after neutral−acid phase fractioning. In this way, 42 g of **9** was obtained in a suitable purity for further reactions from 2.2 kg of dry plant, without chromatographic purification. Oxidation of **9** with selenium dioxide resulted in high stereoselectivity alcohol **10** (66% yield). The ^{1}H NMR spectrum of **10** showed that the proton H-3′ appeared at δ 4.39 ppm as a triplet (J = 3.0 Hz). The multiplicity and the coupling constant were consistent with H-3′ being in the equatorial position (β face), which supported our assignment of the stereochemistry of the C-3′ hydroxy group in **10**. After protecting the hydroxyl group in the form of a *tert*-butyldimethylsilyl ether, the side chain lengthening of **11** was performed. All attempts at alkylation with different alkyl halides were unsuccessful; nevertheless, the condensation of kinetic enolate from **11** with glyoxal dimethylacetal was achieved, giving hydroxy ketone **12** in 95% yield, the mesylate of which underwent elimination with DBU to give the α,β-unsaturated ketone **14**. The *E* configuration of the C(2)−C(3) double bond was established on the basis of the ^{1}H NMR spectrum analysis, which showed two double doublets at δ 6.31 ppm (J = 16.1, 1.3 Hz) and 6.54 ppm (J = 16.1, 4.1 Hz), due to the olefinic protons. Chemoselective reduction of the conjugated double bond was accomplished by following a new methodology described by the present authors.[14] Reduction of **14** with Raney nickel gave **15** in 94% yield.

Ozonolysis of the exocyclic double bond gave diketone **16**, which underwent intramolecular aldol condensation to give the tricyclic enone **17** (Scheme 3). The ^{1}H NMR spectrum of **17** showed that the acetal proton (H-2′) appeared at δ 4.23 ppm as a double doublet (J = 5.1, 3.0 Hz), because of the shielding effect of the ketone carbonyl group. Hydrocyanation of **17** with potassium cyanide, diethylaluminum cyanide, and 18-crown-6 ether[15] afforded, in high stereoselectivity, nitrile **18a,b** as an epimer mixture. **18a** (β epimer) and **18b** (α epimer) were obtained in 75% and 12% yield, respectively, after column chromatography. The configuration of carbon C-16 was assigned on the basis of NOE difference experiments. Irradiation on the C-16 methoxy group of **18a** produced a significant enhancement of the signals corresponding to the proton H-12β.

Acetal isomer **18a** was used to complete the synthetic sequence to facilitate spectroscopic analysis. In this compound, the ketone group is masked as enol ether, which allows the nitrile to be transformed into a hydroxymethyl group by reduction. Subsequent reduction of **18a** with

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DIBAL and ammonium chloride allowed the simultaneous reduction of the nitrile and ester groups, affording hydroxyaldehyde **19** in 93% yield (Scheme 4). Diacetate **21** was obtained after treatment with sodium borohydride and acetylation. Finally, the furan ring opening was accomplished. Exposure of **21** to thiophenol and boron trifluoride etherate in methylene chloride at room temperature for 5 h allowed, for the simultaneous deprotection of the silyl ether group, the opening of the dihydrofuran ring and the subsequent cyclization to the thioacetal derivative **22**. This compound was obtained as an epimer mixture, in 85% yield, the thioether groups of which were sequentially removed. Acetal epimers **23** resulted when **22** was stirred with mercury(II) chloride and mercury oxide in acetonitrile/methanol (1:1) at room temperature for 14 h. Finally, **24** was obtained as an epimer mixture after reductive desulfurization of **23** with nickel boride.

The synthetic sequence from **5a**−**c** to **24** constitutes an AB−ABC−ABCD approach to the enantiospecific synthesis of pentacyclic antitumor quassinoids, which could be competitive with those previously reported.

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Supporting Information Available: Experimental procedures and IR, HRMS, and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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