Analysis of the Products. The yields obtained with 1 and 2 were determined by gas chromatography using an Intersmat IGC 120 DFL chromatograph equipped with an in-flame ionization detector and an OV 17 (10%) column, operating isothermically at 160 °C.

In the case of 3, the products were analyzed by a Perkin-Elmer Series 2/HPLC, using a 5-μm C_{18} column and NaOH/H_2O 80/20 (v/v) as eluent; the flux was 1.2 mL/min.

IR Spectra of Adsorbed Species. General Procedure. The adsorption experiments were carried out under conditions analogous to those described in the experimental procedure. The adsorption time was reduced to one-third the reaction time to avoid decomposition of the adsorbed carbanion.

The solid was filtered and washed with clean solvent to eliminate the physisorption of molecules of reagent and then dried under vacuum. The IR spectra of these solids were recorded on a Perkin-Elmer 599 B IR spectrometer using Perkin-Elmer 3600 data station for the accumulation of spectra (PECDS program).

Registry No. 1, 3084-53-5; 2, 25709-55-1; 3, 1774-47-6; 4 (R = Fu), 98-01-1; 4 (R = C_6H_5), 100-52-7; 4 (R = 2-$NO_2C_6H_4$), 555-16-8; 4 (R = 4-$CH_3C_6H_4$), 104-87-0; 4 (R = 3-$NO_2C_6H_4$), 99-61-6; 4 (R = 4-$CH_3OC_6H_4$), 123-11-5; 4 (R = 4-ClC_6H_4), 104-88-1; 5 (R = 4-$CH_3C_6H_4$), 13107-39-6; 5 (R = 3-$NO_2C_6H_4$), 20697-05-6; 5 (R = 4-$CH_3OC_6H_4$), 6388-72-3; 5 (R = Fu), 2745-17-7; 5 (R = C_6H_5), 96-09-3; 5 (R = 4-$NO_2C_6H_4$), 6388-74-5; 6 (R = Fu), 4561-70-0; 6 (R = C_6H_5), 121-39-1; 6 (R = 4-$NO_2C_6H_4$), 109844-94-2; 6 (R = 4-ClC_6H_4), 75755-52-1; 6 (4-MeC_6H_4), 52788-71-3; 6 (3-$NO_2C_6H_4$), 109318-46-9; KOH, 1310-58-3; K_2CO_3, 584-08-7; $Ba(OH)_2$, 17194-00-2.

An Enantioselective Synthesis of (+)-Picrasin B, (+)-Δ^2-Picrasin B, and (+)-Quassin from the *R*-(-) Enantiomer of the Wieland-Miescher Ketone

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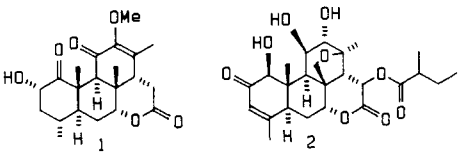
Received June 20, 1989

An enantioselective total synthesis of (+)-picrasin B (1), (+)-Δ^2-picrasin B (11), and (+)-quassin (12) from the *R*-(-) enantiomer of the Wieland-Miescher ketone (3) employed an A-AB-ABC-ABCD sequence to assemble the tetracyclic skeleton. The crucial steps in this sequence relied upon a Diels-Alder reaction of a bicyclic AB dienophile 15 with 1-methoxy-2-methyl-3-((trimethylsilyl)oxy)-1,3-butadiene to obtain a tricyclic diol 16, an α'-oxidation of a tricyclic enone intermediate 20 using manganese(III) acetate in order to introduce the C-11 substituent needed to invert the C-9β stereochemistry, and a free-radical cyclization of an α-bromo acetal 23 in order to introduce a protected δ-lactol as a progenitor of the quassinoid D ring.

Recent interest in the quassinoids[1] culminated in ingenious total syntheses[2] of four tetracyclic members of the C_{20} picrasane family in racemic form by groups led by Grieco[3-5] and by Takahashi.[6] Additional interest in enantioselective routes to the quassinoids began with early investigations by Dias[7] and by Graf[8] who selected various steroids and progressed to other imaginative routes devised by Ziegler[9] who employed (+)-carvone as a homochiral source, by Schlessinger[10] who recognized a solution to the stereochemical problems of the C ring of certain quassinoids in α-D-glucose, and by Fukumoto and Kametani[11] who also reported an approach that paralleled the Schlessinger approach.[10] These enantioselective routes, although attractive vehicles for testing the development of new strategies and new synthetic procedures, have not, as yet, reached fruition in terms of a completed total synthesis.

Scheme I



In developing an enantioselective synthesis[12] of tetracyclic quassinoids such as picrasin B[13] (1) and pentacyclic

(1) Polonsky, J. *Forts. Chem. Org. Naturst.* **1973**, *30*, 101; **1985**, *47*, 221.

(2) For a review of synthetic work in this area, see: Kawada, K.; Kim, M.; Watt, D. S. *Org. Prep. Proc. Int.* **1989**, *21*, 521.

(3) For a synthesis of (±)-quassin, see: (a) Grieco, P. A.; Ferriño, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7587. (b) Vidari, G.; Ferriño, S.; Grieco, P. A. *Ibid.* **1984**, *106*, 3539.

(4) For a synthesis of (±)-castelanolide, see: (a) Grieco, P. A.; Lis, R.; Ferriño, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601. (b) Grieco, P. A.; Lis, R.; Ferriño, S.; Jaw, J. Y. *Ibid.* **1984**, *49*, 2342.

(5) For a synthesis of (±)-klaineanone, see: Grieco, P. A.; Parker, D. T.; Nargund, R. P. *J. Am. Chem. Soc.* **1988**, *110*, 5568.

(6) (a) Miyaji, K.; Nakamura, T.; Hirota, H.; Igarashi, M.; Takahashi, T. *Tetrahedron Lett.* **1984**, *25*, 5299. (b) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Takahashi, T. *Ibid.* **1987**, *28*, 435.

(7) (a) Dias, J. R.; Ramachandra, R. *Tetrahedron Lett.* **1976**, 3685. (b) Dias, J. R.; Ramachandra, R. *J. Org. Chem.* **1977**, *42*, 3584. (c) Dias, J. R.; Ramachandra, R. *Ibid.* **1977**, *42*, 1613. (d) Dias, J. R.; Nassim, B. *Steroids* **1980**, *35*, 405. (e) Nassim, B.; Schlemper, E. O.; Dias, J. R. *Ibid.* **1982**, *39*, 531.

(8) (a) Koch, H. J.; Pfenninger, H.; Graf, W. *Helv. Chim. Acta* **1975**, *58*, 1727. (b) Pfenninger, J.; Graf, W. *Ibid.* **1980**, *63*, 1562.

(9) (a) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730; (b) Ziegler, F. E.; Hwang, K.-J.; Kadow, J. F.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Org. Chem.* **1986**, *51*, 4573.

(10) Schlessinger, R. H.; Wong, J.-W.; Poss, M. A.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 3951.

(11) (a) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1986**, *27*, 1339. (b) Shishido, K.; Takahashi, K.; Fukumoto, K.; Kametani, T.; Honda, T. *J. Org. Chem.* **1987**, *52*, 5704. (c) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Heterocycles* **1988**, *27*, 495.

(12) For a preliminary account of this work, see: Kawada, K.; Kim, M.; Watt, D. S. *Tetrahedron Lett.*, in press.

(13) This quassinoid has also been called "norquassin" and "nigakilactone I" and "similikalactone B".[11c] (a) Viala, B.; Polonsky, J. *C. R. Acad. Sci., Ser. C* **1970**, *271*, 410. (b) Hikino, H.; Ohta, T.; Takemoto, T. *Chem. Pharm. Bull. (Tokyo)* **1970**, *18*, 219. (c) Tresca, J.-P.; Alais, L.; Polonsky, J. *C. R. Acad. Sci., Ser. C.* **1971**, *273*, 601. (d) Hikino, H.; Ohta, T.; Takemoto, T. *Phytochemistry* **1975**, *14*, 2473. (e) Polonsky, J.; Tri, M. V.; Varon, Z.; Prange, T.; Pascard, C.; Sevenet, T.; Pusset, J. *Tetrahedron* **1980**, *36*, 2983. (f) Park, M. H.; Maeda, M.; Komura, H.; Nakanishi, K.; Nomoto, K. *Chem. Pharm. Bull. (Tokyo)* **1987**, *35*, 3082.

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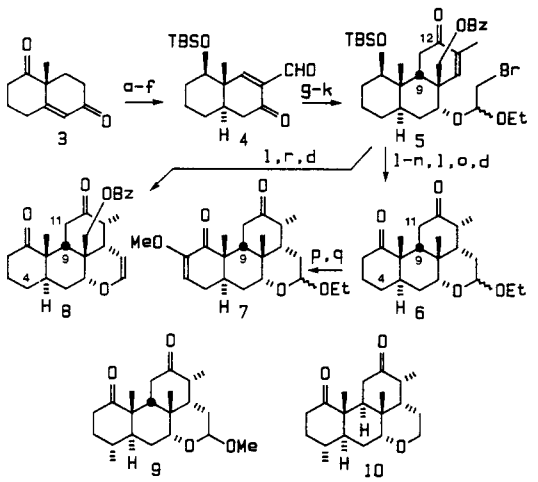
Scheme II[a]

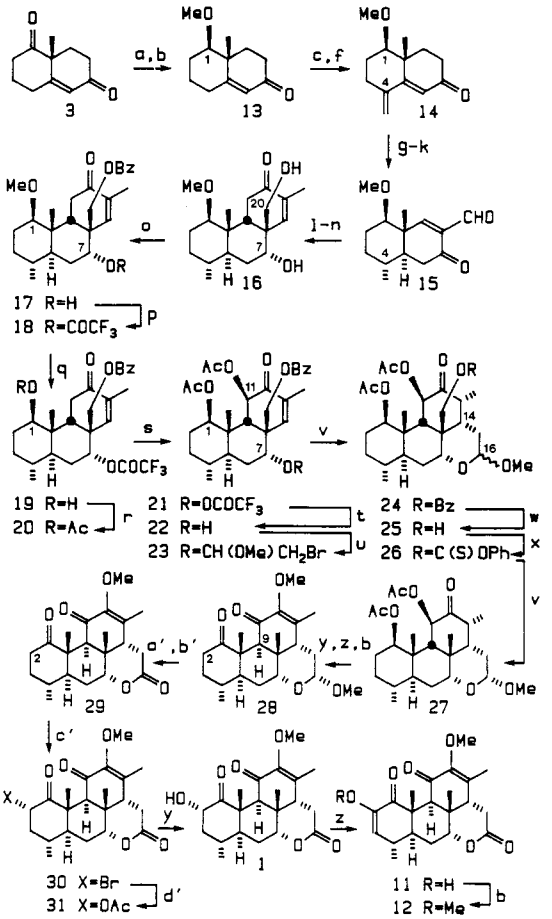


[a] (a) $NaBH_4$, EtOH, 0 °C, 4 h (92%); (b), *t*-$BuMe_2SiCl$, imidazole (85%); (c) Li, NH_3, EtOH (93%); (d) PCC, NaOAc, CH_2Cl_2 (96%); (e) NaH, HCO_2Et, DME, EtOH (cat.) (96%); (f) PhSeCl, $CHCl_3$, Py, followed by 30% H_2O_2 (72%); (g) CH_2=C(OTMS)C-(CH_3)=$CHOCH_3$; (h) $NaAlH_2(OCH_2CH_2OCH_3)_2$, toluene; (i) 0.005 M HCl (83% for steps g, h, i); (j) PhCOCl, DMAP, Py (90%); (k) $BrCH_2CH(OMe)Br$, $PhNMe_2$, CH_2Cl_2 (93%); (l) (*n*-$Bu)_3SnH$, AIBN, benzene, 80 °C (82%); (m) K_2CO_3, MeOH (86%); (n) PhOC(S)Cl, Py (93%); (o) (*n*-$Bu)_4NF$ (56%); (p) NaH, O_2, $P(OEt)_3$ (26%); (q) NaOMe, DMSO, CH_3I (73%); (r) $BF_3{\cdot}Et_2O$ (59%).

quassinoids such as similikalactone D (**2**) in Scheme I, we sought an advanced intermediate that would provide access to both subgroups in homochiral form. Although biological activity resided largely in the pentacyclic subgroup, prudence dictated assembly of the tetracyclic group as a suitable vehicle for testing methodology needed for the pentacyclic series.

We reported[14] a synthesis of a protected tetracyclic diketone **6**, shown in Scheme II, that originated from the *R*-(−) enantiomer of the Wieland–Miescher ketone. The intermediates in this series possessed the unnatural C-9β configuration and the success of this approach hinged upon elevating the oxidation level at C-11 to a ketone stage and subsequently inverting the C-9β stereocenter. However, despite reports[3] of a successful oxodiperoxymolybdenum hexamethylphosphoramide pyridine (MoOPH) oxidation[15] of a bis(enolate) of the related diketone **9** and a successful *m*-chloroperoxybenzoic acid (MCPBA) oxidation of a bis(trimethylsilyl enol ether) derived from the diketone **10**, we were unable to effect oxidation of the C-11 position in **6** or **8**.[16] In addition, the intermediates leading up to diketones **6** and **8** lacked the C-4α methyl group of the picrasane skeleton, and various procedures designed to solve this structural deficiency late in the synthesis failed. We subsequently recast the synthesis in favor of intermediates that incorporated the C-4 methyl group early in the route[17] and intermediates that permitted C-11 oxidation using a manganese(III) acetate procedure.[18] We now report an enantioselective total synthesis of (+)-picrasin B[13] (**1**), (+)-Δ^2-picrasin B[13e] (**11**), and (+)-quassin (**12**) that successfully negotiated these hurdles.

Scheme III[a]



[a] Letters a or b following compound numbers refer to α or β orientations of the C-16 methoxy group. (a) $NaBH_4$ (92%); (b) NaH, MeI (89%); (c) TMSCl, Et_3N (94%); (d) $[CH_2$=$N(CH_3)_2]I$ (85%); (e) CH_3I; (f) 20% NaOH, EtOAc (73% for steps e, f); (g) PhSH, K_2CO_3 (85%); (h) Li, NH_3; (i) PCC (72% for steps h, i); (j) NaH, HCO_2Et (100%); (k) PhSeCl followed by H_2O_2 (77%); (l) CH_2=C-(OTMS)C(CH_3)=$CHOCH_3$; (m) $NaAlH_2(OCH_2CH_2OCH_3)_2$; (n) H_3O^+ (80% for steps l, m, n); (o) PhCOCl, Py DMAP (97%); (p) TFAA, Py (88%); (q) TMSCl, NaI, CH_3CN (92%); (r) Ac_2O, Py (84%); (s) $Mn(OAc)_3$, benzene, 80 °C (89%); (t) $(NH_2)_2C$=S, $NaHCO_3$, EtOH (95%); (u) $PhNMe_2$, $BrCH_2CH(OMe)Br$ (90%); (v) (*n*-$Bu)_3SnH$ (70%); (w) K_2CO_3, MeOH, 0 °C (52%); (x) PhOC-(S)Cl, Py (78%); (y) K_2CO_3, MeOH, 25 °C (51%); (z) DMSO, TFAA followed by Et_3N (62%); (a′) 60% aqueous HOAc; (b′) Ag_2-CO_3, Celite (59% for steps a′, b′); (c′) $CuBr_2$, MeOH (44%); (d′) Me_4NOAc (49%).

Several additional considerations also guided the redesign of the original synthetic route. We sought to avoid any need for the selective manipulation of both a C-12 ketone and a D ring δ-lactone, a problem that we had encountered in a previous route. Consequently, we required a procedure for the direct introduction of a protected δ-lactol in the presence of a C-12 ketone, and the crucial step in this plan was a free-radical cyclization[14] of a bromo acetal[19] such as **5** in Scheme II to deliver a pro-

(14) Kim, M.; Gross, R. S.; Sevestre, H.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1988**, *53*, 93.

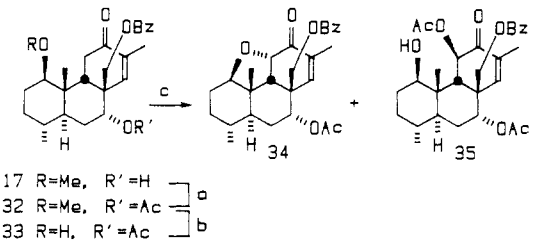
(15) Mimoun, H.; Seree de Roch, I.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, 1481.

(16) Efforts to effect the oxidation of the bis(enolate) of **6** directly to a bis(diosphenol), efforts to employ the lead tetraacetate or MCPBA oxidation of a bis(trimethylsilyl enol ether) derived from **6**, efforts to prepare a C-2,11 bis(hydroxymethylene), bis(enamine), or bis(enone) adduct from **6**, efforts to block the C-13 position (e.g., bis(phenylsulfenylation) at C-2 and C-13) prior to an enolate oxidation at C-11, or efforts to oxidize a C-2 blocked derivative such as **7** at C-11 were unrewarding. In a similar vein, other advanced intermediates such as the diketone **8** in Scheme II that differed from **6** in the nature of the δ-lactol protecting group and the presence of the C-20 benzoate were recalcitrant toward C-11 oxidation.

(17) Kim, M.; Kawada, K.; Watt, D. S. *Synth. Commun.* **1989**, *19*, 2017.

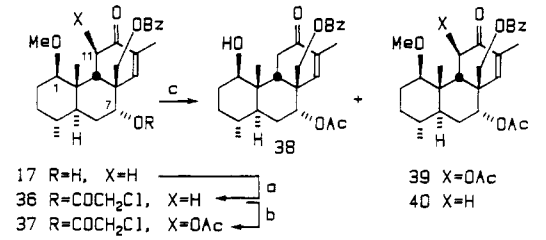
(18) Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839.

Scheme IV[a]



[a] (a) Ac_2O, Py (90%); (b) TMSCl, NaI (96%); (c) $Mn(OAc)_3$, benzene, 80 °C (73% of **34** and 5% of **35**).

Scheme V[a]



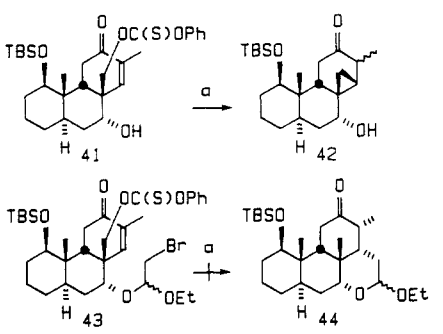
[a] (a) $(ClCH_2CO)_2O$, Py (94%); (b) $Mn(OAc)_3$, benzene, 80 °C (63%); (c) TMSCl, NaI (18% of **38**, 32% of **39**, 12% of **40**).

tected δ-lactol. As shown in Scheme III, we introduced the C-4α methyl group after reduction of the Wieland–Miescher ketone[20] (**3**) and protection of the C-1β hydroxyl as the methyl ether **13**. Other more easily removable C-1 protecting groups (e.g., allyl ether, *tert*-butyldimethylsilyl ether) proved incompatible with operations later in the synthesis necessitating a C-1β methyl ether. In order to introduce the C-4α methyl group,[17] we employed the dienone **14** as the key intermediate. The Diels–Alder reaction of the dienophile **15** with 1-methoxy-2-methyl-3-((trimethylsilyl)oxy)-1,3-butadiene[21] provided, following reduction and hydrolysis, the tricyclic diol **16** in excellent yield. Protection of the C-20 alcohol in **16** as the benzoate and the C-7α alcohol as the trifluoroacetate ester furnished the enone **18**.

Although manganese(III) acetate was a reliable oxidant for the C-11 oxidation of tricyclic enones similar to **18**,[18] its selection in the present circumstance raised the issue of the compatibility of this procedure with C-1 functionality, a structural feature that was not present in previous studies. We found that manganese(III) acetate was ineffectual in the presence of sterically bulky C-1 protecting groups such as acetals or *tert*-butyldimethylsilyl ethers and was equally incompatible with free hydroxyl groups at either the C-1β or C-7α positions, a fact that dictated protection of both hydroxyl groups in the diol **16**. For example, the oxidation of **33** in Scheme IV led to the tetrahydrofuran derivative **34**, and although **34** was an attractive candidate for further manipulation, we were unable to utilize it in a productive fashion.

After determining that the manganese(III) acetate oxidation would accommodate either a C-1β methoxy or a C-1β acetoxy group, we examined the order in which to conduct the C-11 oxidation and the C-1 deprotection steps. In the former case, we found that the oxidation of **36** in Scheme V secured the α′-acetoxy enone **37**, but the deprotection of the C-1β methoxy group was thwarted by the presence of the C-11β acetate. Competitive reduction of the C-7α chloroacetate and/or the α′-acetoxy enone functionality required a route in which C-1 deprotection preceded the C-11 oxidation process.

Scheme VI[a]



[a] (a) $(n\text{-Bu})_3SnH$.

Consequently, as shown in Scheme III, we converted the C-1β methyl ether **18** to a C-1β acetate **20** and employed a manganese(III) oxidation to acquire the C-1β,11β diacetate **21**. The accessibility of the exo-face of the tricyclic enone **20** and the $J_{9,11}$ coupling constant of 4 Hz were consistent with the C-11β stereochemical assignment in α′-acetoxy enone **21**. Selective saponification of the C-7α trifluoroacetate in **21** using sodium bicarbonate and thiourea and the conversion to the α-bromo acetal **23** permitted the closure of the D ring using a free-radical cyclization[14] to afford the protected δ-lactol as a separable mixture of C-16 epimers **24a** (C-16α methoxy group) and **24b** (C-16β methoxy group).

We based the stereochemical assignments at C-13, C-14, and C-16 in δ-lactols **24** on the following observations. First, we assumed that the α-oriented bromo acetal appendage in **23** would guarantee the desired C-14β(H) stereochemistry, a point that was confirmed later in the synthesis by comparison with the natural quassinoids. Secondly, we assigned the C-13 stereochemistry on the basis of ^1H NMR data and MM2 calculations. The ^1H NMR for diketone **6** (Scheme II) revealed that both C-16 epimers had $J_{13,14}$ values of less than 5 Hz, consistent with a dihedral angle of approximately 30° and a conformation in which the C ring preferred a twist-boat conformation bearing a C-13α methyl group. Among the possible conformations of diketones **6** or **24** in which either the B, C, or D ring was a twist-boat, MM2 calculations also indicated that the conformer having the C ring as a twist-boat with a C-13α methyl group was the most stable. Finally, we assigned the C-16 stereochemistry by noting that the ^1H NMR signals for the equatorial C-16α(H) proton in the δ-lactols **24b**, **25b**, **26b**, and **27b** appeared at lower field[22] than the axial C-16β(H) proton in the δ-lactols **24a**, **25a**, **26a**, and **27a**.

Selective saponification of the C-20 benzoate in **24** (as a mixture of C-16 epimers) furnished the C-20 alcohol **25**, the pivotal intermediate that we planned to utilize in the synthesis of both the tetracyclic and pentacyclic quassinoid families. The application of this intermediate in the former connection required the reduction of the C-8β hydroxymethyl group to a simple C-8β angular methyl group, a goal

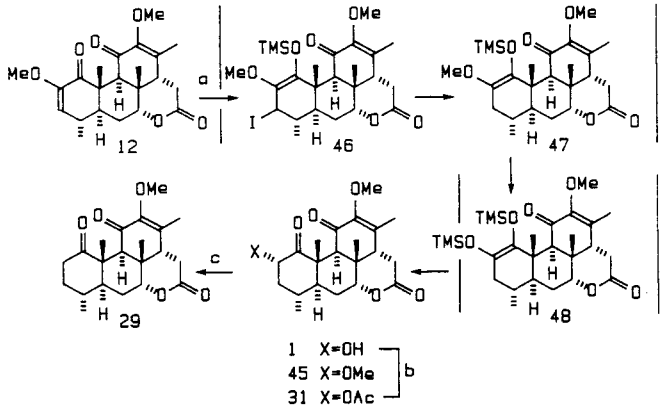
(19) For related free-radical cyclizations of α-bromo acetals, see: (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *Ibid.* **1983**, *105*, 3741. (c) Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1984**, *25*, 4317. (d) Hutchinson, J. H.; Pattenden, G.; Myers, P. L. *Tetrahedron Lett.* **1987**, *28*, 1313.

(20) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1612. (c) Hajos, Z. G.; Parrish, D. R. *Ibid.* **1974**, *39*, 1615.

(21) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

(22) Kotowycz, G.; Lemieux, R. U. *Chem. Rev.* **1973**, *73*, 669.

Scheme VII[a]



[a] (a) TMSCl, NaI (42%); (b) Ac_2O, Py (77%); (c) Zn, HOAc (78%).

that employed the tri-*n*-butyltin hydride reduction[23] of a C-20 thionocarbonate **26** as the key operation. We should also note that an effort to reduce the C-20 hydroxymethyl group earlier in the sequence led, in the case of enone **41** in Scheme VI to the cyclopropane **42**, and an effort to telescope the free-radical cyclization of the α-bromo acetal and the thionocarbonate reduction into the same step as in the conversion of **43** to **44** was also unsuccessful and dictated a stepwise solution to these problems.

Further saponification of the C-1β and C-11β acetate groups in the C-16α epimer **27a**, Swern oxidation,[24] and methylation provided the *O*-methyldiosphenol **28** in which the correct C-9α stereochemistry emerged for the first time. It was surprising that the analogous saponification of the C-16β epimer **27b** led to the complete destruction of the starting material, but since we could equilibrate the C-16β epimer **27b** in favor of the more tractable C-16α epimer **27a**, this point was not troublesome. At this stage, we planned to employ an enolate oxidation procedure to introduce either the C-2 hydroxyl group or the C-2 keto group, but unfortunately, *O*-methyldiosphenol **28** would not survive exposure to lithium diisopropylamide or autooxidation with sodium hydride and oxygen.

Subsequent hydrolysis of the protected δ-lactol in **28** and silver carbonate[25] oxidation provided 2-deoxypicrasin B (**29**), but again application of various procedures for the oxidation of the C-2 position in **29** to provide an α-ketol or diosphenol were unproductive. Exposure of **29** to lithium bis(trimethylsilyl)amide and chlorotrimethylsilane followed by *m*-chloroperoxybenzoic acid, for example, led to the selective oxidation of the C-13 methyl group. With meager supplies of synthetic **29** in hand, we undertook a synthesis of **29** from a readily available quassinoid, (+)-quassin (**12**). Using chlorotrimethylsilane and sodium iodide[26] in acetonitrile, we effected the regioselective reduction and demethylation of the *O*-methyldiosphenol in the A ring of **12** and secured (+)-picrasin B[13] (**1**) in 42% yield along with the α-methoxy ketone **45** in 9% yield as shown in Scheme VII.

The reduction of **12** by iodotrimethylsilane, generated in situ from chlorotrimethylsilane and sodium iodide, proceeded with the rapid formation of iodine; the reduction in the presence of acetonitrile-d_3 led to no deuterium incorporation, and the reduction succeeded in the presence of 0.5 equiv of water. We suggest that the mechanism of this reduction involved the 1,4-addition of iodotrimethylsilane[27] to the *O*-methyldiosphenol functionality in the A ring of **12** to provide the intermediate β-iodo trimethylsilyl enol ether **46** in Scheme VII. The C-13 methyl group in **12** retarded addition to the *O*-methyldiosphenol functionality in the C ring. Hydrogen iodide, produced by the hydrolysis of iodotrimethylsilane by trace amounts of water present in commercial samples of acetonitrile or acetonitrile-d_3, provided the reducing agent for the further conversion of **46** to **47**. However, iodotrimethylsilane was essential for this reduction, and hydrogen iodide alone was not sufficient to reduce **12** to **1**. Further demethylation of the C-2 methoxy group in **47** and hydrolysis furnished (+)-picrasin B (**1**) and hydrolysis of the intermediate **47** produced the α-methoxy ketone **45**.

The conversion of **1** to the α-acetoxy ketone **31** and reduction of **31** using zinc in acetic acid[28] secured (+)-2-deoxypicrasin B (**29**) that was identical in all respects, including molecular rotation ($[\alpha]_D$ = +12° for **29** derived from **12**) to material prepared in Scheme III ($[\alpha]_D$ = +10.5° for **29** derived from **3**). Given the small amount of **29** available from **3**, the rotations are well within experimental error. With this relay compound available and its identity with synthetic (+)-2-deoxypicrasin B (**29**) firmly established, we completed a total synthesis of (+)-picrasin B (**1**) through a sequence involving bromination at C-2, acetolysis of the α-bromo ketone[29] **30**, and hydrolysis of the α-acetoxy ketone **31**. Alternate procedures (e.g., lead tetraacetate oxidation) designed to elevate the C-2 oxidation level were unproductive. Swern oxidation[24] of **1** in turn furnished (+)-Δ²-picrasin B (**11**), and O-methylation provided (+)-quassin (**12**). With the completion of these enantioselective syntheses of three tetracyclic members of the quassinoid family, we can proceed to tackle the more challenging pentacyclic quassinoids using the homochiral intermediate **25** in Scheme III as an attractive departure point.

Experimental Section

7α-Hydroxy-8β-(hydroxymethyl)-1β-methoxy-13-methyl-19-nor-9β-podocarp-13-en-12-one (16). To 1.00 g (4.23 mmol) of dienophile[17] **15** in 10 mL of anhydrous benzene at 25 °C under a nitrogen atmosphere was added 1.81 mL (9.3 mmol) of 1-methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene.[21] The solution was stirred for 15 h at 25 °C. To 3.7 mL (12.7 mmol) of 3.4 M sodium bis(2-methoxyethoxy)aluminum hydride in 10 mL toluene at 0 °C was added dropwise the crude Diels–Alder product. The solution was stirred for 1 h at 0 °C, and the reaction was quenched by the slow addition of 23.3 mL of 1 M hydrochloric acid solution and 58 mL of THF. The mixture was stirred for 15 min at 25 °C and filtered through Celite. The Celite was washed with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, concentrated, and dissolved in 53 mL of THF. To this solution was added 13.2 mL of 0.005 M hydrochloric acid solution, and the mixture was stirred for 17 h at 25 °C. The product was diluted with ethyl acetate, washed with brine, dried, concentrated, and crystallized from ether to afford 1.10 g (80%) of **16**: mp 225–228 °C; $[\alpha]_D$ −67.5° (*c* 1.24 × 10^{-2}, methanol); IR (KBr) 3410, 2920, 1530 cm^{-1}; ^1H NMR (CD_3OD) δ 0.84 (d, *J* =

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5 Hz, 3, C-4α CH_3), 1.06 (s, 3, C-10β CH_3), 1.79 (s, 3, C-13 vinylic CH_3), 3.12 (dd, J = 5 and 10 Hz, 1, C-1α CH), 3.28 (s, 3, OCH_3), 3.59 and 3.68 (AB q, J = 10 Hz, 2, CH_2OH), 3.85 (t, J = 3 Hz, 1, C-7β H), 6.59 (s, 1, C-14 H); exact MS calcd for $C_{19}H_{30}O_4$ 322.2145, found 322.2144.

8β-((Benzoyloxy)methyl)-7α-hydroxy-1β-methoxy-13-methyl-19-nor-9β-podocarp-13-en-12-one (17). To 610 mg (1.89 mmol) of **16** in 20 mL of anhydrous pyridine was added 369 mg (3 mmol) of 4-(*N*,*N*-dimethylamino)pyridine at 0 °C. The mixture was stirred for 5 min at 0 °C, and 548.5 μL (4.7 mmol) of benzoyl chloride was added at 0 °C. The solution was stirred for 18 h at 25 °C. The product was diluted with ethyl acetate, washed with 3 M hydrochloric acid and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel using 4:1 ethyl acetate–hexane to afford 783 mg (97%) of **17**: $[\alpha]_D$ −63° (c 1.2 × 10^{-3}, $CHCl_3$); IR (TF) 2920, 1708, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, J = 5 Hz, 3, C-4α CH_3), 1.04 (s, 3, C-10β CH_3), 1.87 (s, 3, C-13 CH_3), 3.25 (dd, J = 5 and 10 Hz, 1, C-1α CH), 3.30 (s, 3, OCH_3), 3.91 (t, J = 3 Hz, 1, C-7β H), 4.38 and 4.48 (AB q, J = 12 Hz, 2, CH_2OBz), 6.59 (s, 1, C-14 H), 7.41–7.71 (m, 5, ArH).

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 73.00; H, 8.12.

8β-((Benzoyloxy)methyl)-1β-methoxy-13-methyl-7α-(trifluoroacetoxy)-19-nor-9β-podocarp-13-en-12-one (18). To 1.00 g (2.3 mmol) of **17** in 10 mL of anhydrous pyridine was added 487 μL (3.45 mmol) of trifluoroacetic anhyride at −20 °C under a nitrogen atmosphere. The solution was stirred for 1 h at −20 °C and poured into 50 mL of cold 3 M hydrochloric acid solution. The product was extracted with ethyl acetate, and the combined extracts were washed with 3 M hydrochloric acid solution and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel with 1:4 ethyl acetate–hexane to afford 1.06 g (88%) of **18**: IR (TF) 2920, 1760, 1715, 1670 cm^{-1}; $[\alpha]_D$ −77° (c 1.14 × 10^{-2}, benzene); ^1H NMR ($CDCl_3$) δ 0.82 (d, J = 5 Hz, 3, C-4α CH_3), 1.12 (s, 3, C-10β CH_3), 1.80 (s, 3, C-13 CH_3), 3.18 (dd, J = 4 and 10 Hz, 1, C-1α CH), 3.3 (s, 3, OCH_3), 4.29 and 4.74 (AB q, J = 12 Hz, 2, C-8 CH_2OBz), 5.41 (t, J = 3 Hz, 1, C-7β H), 6.5 (s, 1, C-14 H), 7.45–7.66 and 8.0–8.1 (m, 5, ArH).

Anal. Calcd for $C_{28}H_{33}F_3O_6$: C, 64.36; H, 6.36. Found: C, 64.23; H, 6.39.

8β-((Benzoyloxy)methyl)-1β-hydroxy-13-methyl-7α-(trifluoroacetoxy)-19-nor-9β-podocarp-13-en-12-one (19). To 1.06 g (2.03 mmol) of **18** in 30 mL of anhydrous acetonitrile was added 3.00 g (20.3 mmol) of sodium iodide followed by 2.6 mL (20.3 mmol) of chlorotrimethylsilane at 25 °C under a nitrogen atmosphere. The solution was stirred for 20 h at 25 °C. The reaction was quenched by adding 5 mL of 5% sodium thiosulfate solution. The solution was extracted using ethyl acetate, and the combined extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The product was chromatographed on silica gel with 1:2 ethyl acetate–hexane to afford 950 mg (92%) of **19**: IR (TF) 3400, 2920, 1778, 1710, 1660 cm^{-1}; $[\alpha]_D$ −37° (c 1.28 × 10^{-2}, dichloromethane); ^1H NMR ($CDCl_3$) δ 0.81 (d, J = 4 Hz, 3, C-4α CH_3), 1.15 (s, 3, C-10β CH_3), 1.79 (s, 3, C-13 CH_3), 3.71 (t, J = Hz, 1, C-1 CH), 4.32 and 4.72 (AB q, J = 12 Hz, 2, C-8 CH_2OBz), 5.42 (t, J = 3 Hz, 1, C-7β H), 6.48 (s, 1, C-14 H), 7.44–7.68 and 7.99–8.09 (m, 5, ArH).

Anal. Calcd for $C_{27}H_{31}F_3O_6$: C, 63.77; H, 6.14. Found: C, 63.63; H, 6.21.

1β-Acetoxy-8β-((benzoyloxy)methyl)-13-methyl-7α-(trifluoroacetoxy)-19-nor-9β-podocarp-13-en-12-one (20). To 900 mg (1.77 mmol) of **19** in 20 mL of anhydrous pyridine was added at 0 °C under a nitrogen atmosphere 8.35 mL (88.5 mmol) of acetic anhydride. The solution was stirred for 18 h at 25 °C, and the reaction was quenched by dilution with 50 mL of cold 3 M hydrochloric acid solution. The product was extracted with ethyl acetate, and the combined extracts were washed with 3 M hydrochloric acid solution and brine, dried over anhydrous magnesium sulfate, and concentrated. The product was chromatographed on silica gel with 1:2 ethyl acetate–hexane to afford 820 mg (84%) of **20**: $[\alpha]_D$ −41° (c 1.1 × 10^{-2}, benzene); IR (TF) 2950, 1782, 1735, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, J = 5 Hz, 3, C-4α CH_3) 1.26 (s, 3, C-10β CH_3), 1.79 (s, 3, C-13 CH_3), 2.02 (s, 3, $OCOCH_3$), 4.32 and 4.74 (AB q, J = 12 Hz, C-8 CH_2OBz), 4.78 (dd, J = 5 and 10 Hz, C-1α H), 5.4 (t, J = 3 Hz, 1, C-7β H), 6.46 (s, 1, C-14 H), 7.45–7.7 and 8.0–8.1 (m, 5, ArH).

Anal. Calcd for $C_{29}H_{33}F_3O_7$: C, 63.27; H, 6.04. Found: C, 63.37; H, 6.05.

8β-((Benzoyloxy)methyl)-1β,11β-diacetoxy-13-methyl-7α-(trifluoroacetoxy)-19-nor-9β-podocarp-13-en-12-one (21). To 910 mg (1.65 mmol) of **20** in 400 mL of anhydrous benzene was added 7.6 g (12.87 mmol) of manganese triacetate in six portions with intervals of 2 h while the mixture was refluxed under a Dean–Stark trap. The mixture was refluxed an additional 15 h. After cooling, the mixture was filtered through Celite, and the residue was washed with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The product was chromatographed on silica gel with 2:1 hexane–ether to afford 720 mg (89%) of **21**: $[\alpha]_D$ +21.0° (c 9.65 × 10^{-3}, benzene); IR (TF) 2900, 1778, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (d, J = 4 Hz, 3, C-4α CH_3), 1.27 (s, 3, C-10β CH_3), 1.95 (s, 3, C-13 CH_3), 2.08 (s, 3, $OCOCH_3$), 2.10 (s, 3, $OCOCH_3$), 2.67 (d, J = 4 Hz, 1, C-9β H), 4.20 and 4.80 (AB q, J = 10 Hz, 2, CH_2OBz), 4.6 (dd, J = 3 Hz and 8 Hz, 1, C-1α H), 5.39 (d, J = 4 Hz, 1, C-11α H), 5.82 (t, J = 7 Hz, 1, C-7β H), 6.69 (s, 1, C-14 H), 7.45–7.68 and 8.0–8.1 (m, 5, ArH); exact mass spectrum calcd for $C_{31}H_{35}F_3O_9$ 608.2234, found 608.2231.

8β-((Benzoyloxy)methyl)-1β,11β-diacetoxy-7α-hydroxy-13-methyl-19-nor-9β-podocarp-13-en-12-one (22). To 720 mg (1.18 mmol) of **21** in 20 mL of absolute ethanol at 25 °C under a nitrogen atmosphere were added 198 mg (2.60 mmol) of thiourea and 198 mg (2.36 mmol) of sodium bicarbonate. The mixture was stirred for 1.5 h at 25 °C. The product was diluted with ethyl acetate, washed with 3 M hydrochloric acid solution, saturated sodium bicarbonate solution, and brine, dried over anhydrous magnesium sulfate, and concentrated. The product was chromatographed on silica gel with 1:2 ethyl acetate–hexane to afford 573 mg (95%) of **22**: $[\alpha]_D$ +44.0° (c 1.90 × 10^{-2}, dichloromethane); IR (TF) 3460, 2910, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 and 0.84 (d, J = 5 Hz, 3, diastereomeric C-4α CH_3), 1.12 and 1.14 (s, 3, diastereomeric C-10β CH_3), 1.84 and 1.91 (s, 3, diastereomeric C-13 CH_3), 1.98 and 2.02 (s, 3, diastereomeric C-1 OAc), 2.08 and 2.14 (s, 3, diastereomeric C-11 $OCOCH_3$), 2.69 (d, J = 4 Hz, 1, C-9β H for one isomer), 3.05–3.14 and 3.62–3.68 (m, 1, diastereomeric OH), 4.05–4.90 (m, 4, C-1α H, CH_2OBz, C-7β H), 5.26 (d, J = 2 Hz, 1, C-11 H of one isomer), 5.39 (d, J = 4 Hz, 1, C-11 H of one isomer), 6.05 and 6.88 (s, 1, diastereomeric C-14 H), 7.42–7.68 and 8.0–8.12 (m, 5, ArH).

Anal. Calcd for $C_{29}H_{36}O_8$: C, 67.95; H, 7.08. Found: C, 67.86; H, 7.13.

8β-((Benzoyloxy)methyl)-7α-(2-bromo-1-methoxyethoxy)-1β,11β-diacetoxy-13-methyl-19-nor-9β-podocarp-13-en-12-one (23). To 200 mg (0.39 mmol) of **22** in 2 mL of anhydrous dichloromethane at 0 °C under a nitrogen atmosphere was added 173 μL (1.36 mmol) of *N*,*N*-dimethylaniline and 175 μL (1.36 mmol) of 1,2-dibromoethyl methyl ether (bp 83–87 °C (43 mm); prepared by bubbling methyl vinyl ether to a dichloromethane solution of bromine). The solution was stirred for 30 min at 0 °C and for 15 h at 25 °C. The mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid solution, water, and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel with 1:2 ethyl acetate–hexane to afford 229 mg (90%) of **23**: IR (TF) 2910, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 and 0.81 (d, J = 6 Hz, 3, diastereomeric C-4α CH_3), 1.24 and 1.25 (s, 3, diastereomeric C-10 CH_3), 2.04 and 2.05 (s, 3, diastereomeric $OCOCH_3$), 2.07 (s, 3, diastereomeric $OCOCH_3$), 2.62 and 2.69 (d, J = 4 Hz, 1, diastereomeric C-9β H), 3.18 and 3.36 (s, 3, diastereomeric OCH_3), 3.31–3.42 (m, 2, CH_2Br), 4.19–4.82 (m, 5, C-1α H, C-7β H, $CH(OCH_3)$, C-8 CH_2OBz), 5.4 and 5.46 (d, J = 4 Hz, 1, diastereomeric C-11 H), 6.75 and 6.77 (s, 1, diastereomeric C-14 H), 7.42–7.68 and 8–8.1 (m, 5, ArH).

Anal. Calcd for $C_{32}H_{41}BrO_9$: C, 59.17; H, 6.36. Found: C, 58.91; H, 6.45.

20-(Benzoyloxy)-1β,11β-diacetoxy-16α-methoxy-9β-picrasan-12-one (24a) and (10*R*)-20-(Benzoyloxy)-1β,11β-diacetoxy-16β-methoxy-9β-picrasan-12-one (24b). To 290 mg (0.44 mmol) of **23** in 25 mL of anhydrous benzene under a nitrogen atmosphere were added 7 mg (0.04 mmol) of 2,2′-azobisiso-

butyronitrile and 156 μL (0.58 mmol) of tri-*n*-butyltin hydride in 150 μL of benzene in five portions at 30-min intervals while the mixture was refluxed. After cooling, the mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel using 4:1 dichloromethane–ethyl acetate to afford 93 mg (37%) of **24a** and 84 mg (33%) of **24b**. Data for **24a**: IR (TF) 2910, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3, C-4α CH_3), 1.06 (d, J = 6 Hz, 3, C-13α CH_3), 1.19 (s, 3, C-10β CH_3), 1.98 (s, 3, $OCOCH_3$), 2.01 (s, 3, $OCOCH_3$), 2.40–2.52 (m, 1, C-14 H), 2.92 (d, J = 7 Hz, 1, C-9β H), 3.28 (s, 3, OCH_3), 3.08–3.22 (m, 1, C-13β H), 3.74–3.84 (br s, 1, C-7β H), 4.35–4.50 (m, 4, C-1α H, C-16β H, CH_2OBz), 5.69 (d, J = 7 Hz, 1, C-11 H), 7.44–7.66 and 7.98–8.15 (m, 5, ArH); exact mass spectrum calcd for $C_{31}H_{39}O_8$ $[M - CH_3O]^+$ 539.2647, found 539.2647. Data for **24b**: IR (TF) 2940, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, J = 6 Hz, 3, C-4α CH_3), 1.10 (d, J = 7 Hz, C-13α CH_3), 1.25 (s, 3, C-10β CH_3), 1.99 (s, 3, $OCOCH_3$), 2.2 (s, 3, $OCOCH_3$), 2.35–2.49 (m, 1, C-14 H), 2.50 (d, J = 12 Hz, 1, C-9β CH), 2.99–3.11 (m, 1, C-13 H), 3.4 (s, 3, OCH_3), 3.62–3.71 (br s, 1, C-7β H), 4.41 and 4.64 (AB q, J = 12 Hz, 2, CH_2OBz), 4.46 (dd, J = 3 and 10 Hz, 1, C-1α H), 5.08 (dd, J = 5 and 12 Hz, 1, C-16α H), 6.24 (d, J = 12 Hz, 1, C-11 H), 7.44–7.7 and 7.98–8.12 (m, 5, ArH); exact mass spectrum calcd for $C_{31}H_{38}O_8$ $[M - CH_4O]^+$ 538.2568, found 538.2569.

1β,11β-Diacetoxy-20-hydroxy-16-methoxy-9β-picrasan-12-one (25). To 76 mg (0.13 mmol) of **24** as a mixture of C-16 epimers in 800 μL of anhydrous methanol at 0 °C under an argon atmosphere was added 27 mg (0.2 mmol) of potassium carbonate. The mixture was stirred for 6 h at 0 °C. The product was diluted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel with 2:1 ethyl acetate–hexane to afford 32 mg (52%) of **25**. Data for **25a**: IR (TF) 3620, 1745, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3, C-4α CH_3), 1.04 (d, J = 6.5 Hz, 3, C-13 CH_3), 1.24 (s, 3, C-10β CH_3), 1.93 (s, 3, $OCOCH_3$), 2.02 (s, 3, $OCOCH_3$), 2.18 (s, 1, OH), 2.50–2.62 (m, 1, C-14 H), 2.82 (d, J = 8 Hz, C-9β H), 3.06–3.2 (m, 1, C-13 H), 3.27 (s, 3, OCH_3), 3.46 and 3.89 (AB q, J = 11 Hz, 2, CH_2OH), 3.52–3.60 (br s, 1, C-7β H), 4.34–4.48 (m, 2, C-1α H, C-16β H), 5.6 (d, J = 11 Hz, 1, C-11 H); exact mass spectrum calcd for $C_{25}H_{38}O_8$ 466.2568, found 466.2567. Data for **25b**: IR (TF) 3600, 3450, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3, C-4α CH_3), 1.04 (d, J = 6.5 Hz, 3, C-13 CH_3), 1.22 (s, 3, C-10 CH_3), 1.98 (s, 3, $OCOCH_3$), 2.16 (s, 3, $OCOCH_3$), 2.43 (d, J = 11 Hz, C-9 CH), 2.4–2.55 (m, 1, C-14 CH), 3.08–3.20 (m, 1, C-13 H), 3.48 (s, 3, OCH_3), 3.50–3.60 (br s, 1, C-7β H), 3.72 and 3.84 (AB q, J = 11 Hz, 2, CH_2OH), 4.45 (dd, J = 3 and 12 Hz, 1, C-1α H), 5.00 (dd, J = 4 and 11 Hz, 1, C-16 H), 6.18 (d, J = 12 Hz, 1, C-11 H); exact mass spectrum calcd for $C_{25}H_{38}O_8$ 466.2568, found 466.2567.

1β,11β-Diacetoxy-20-((phenoxythiocarbonyl)oxy)-16-methoxy-9β-picrasan-12-one (26). To 40 mg (0.08 mmol) of **25** in 600 μL of dichloromethane at 0 °C under a nitrogen atmosphere were added 23.7 μL (0.17 mmol) of phenyl chlorothionoformate and 41 μL (0.51 mmol) of anhydrous pyridine. The solution was stirred for 3.5 h at 25 °C. The product was diluted with dichloromethane, washed with 1 M hydrochloric acid solution, saturated sodium bicarbonate solution, and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel with 1:3 ethyl acetate–hexane to afford 40 mg (78%) of **26**. Data for **26a**: IR (TF) 2920, 1745, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, J = 4 Hz, 3, C-4α CH_3), 1.04 (d, J = 6 Hz, 3, C-13α CH_3), 1.18 (s, 3, C-10β CH_3), 1.94 (s, 3, $OCOCH_3$), 2.04 (s, 3, $OCOCH_3$), 2.32–2.48 (m, 1, C-14 H), 2.73 (d, J = 8 Hz, 1, C-9β H), 2.95–3.10 (m, 1, C-13β H), 3.27 (s, 3, OCH_3), 3.72–3.80 (br s, 1, C-7β H), 4.32–5.72 (m, 4, C-1α H, C-16β H, $CH_2OCSOPh$), 5.60 (d, J = 8 Hz, 1, C-11 H), 7.1–7.5 (m, 5 ArH); exact mass spectrum calcd for $C_{32}H_{42}O_9S$ 602.2551, found 602.2550. Data for **26b**: IR (TF) 2920, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 5 Hz, 3, C-4α CH_3), 1.01 (d, J = 6 Hz, 3, C-13α CH_3), 1.21 (s, 3, C-10β CH_3), 1.96 (s, 3, $OCOCH_3$), 2.14 (s, 3, $OCOCH_3$), 2.29 (d, J = 12 Hz, 1, C-9 H), 2.25–2.4 (m, 1, C-14 H), 2.7–2.82 (m, 1, C-13 H), 3.45 (s, 3, OCH_3), 3.56–3.64 (br s, 1, C-7β H), 4.42 (dd, J = 3 and 9 Hz, 1, C-1α H), 4.59 and 4.74 (AB q, J = 12 Hz, 2, $CH_2OCSOPh$), 5.02 (dd, J = 4 and 11 Hz, 1, C-16α H), 6.18 (d, J = 12 Hz, 1, C-11 H), 7.05–7.15 and 7.25–7.50 (m, 5, ArH); exact mass spectrum calcd for $C_{32}H_{42}O_9S$ 602.2551, found 602.2550.

1β,11β-Diacetoxy-16-methoxy-9β-picrasan-12-one (27). To 40 mg (0.066 mmol) of **26** in 10 mL of anhydrous benzene at 25 °C under a nitrogen atmosphere were added 1 mg (0.006 mmol) of 2,2′-azobisisobutyronitrile and 58.6 μL (0.21 mmol) of tri-*n*-butyltin hydride in 60 μL of benzene in six portions at 20-min intervals while the reaction mixture was refluxed. After cooling, the solution was diluted with ethyl acetate, washed with 3 M hydrochloric acid solution, saturated sodium bicarbonate solution, and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel with 1:2 ethyl acetate–hexane to afford 20 mg (69%) of **27**. Data for **27a**: IR (TF) 2920, 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, J = 4 Hz, 3, C-4α CH_3), 1.03 (d, J = 6 Hz, 3, C-13α CH_3), 1.19 (s, 3, C-10β CH_3), 1.33 (s, 3, C-8β CH_3), 1.97 (s, 3, $OCOCH_3$), 2.0 (s, 3, $OCOCH_3$), 2.35 (d, J = 10 Hz, 1, C-9β H), 3.00–3.15 (m, 1, C-13β H), 3.28 (s, 3, OCH_3), 3.61–3.69 (br s, 1, C-7β H), 4.42–4.55 (m, 2, C-1α H, C-16β H), 5.68 (d, J = 10 Hz, 1, C-11 H); exact mass spectrum calcd for $C_{24}H_{34}O_6$ $[M - CH_4O]^+$ 418.2357, found 418.2357. Data for **27b**: IR (TF) 2920, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, J = 5 Hz, 3, C-4α CH_3), 1.09 (d, J = 7 Hz, 3, C-13α CH_3), 1.23 (s, 3, C-10β CH_3), 1.39 (s, 3, C-8β CH_3), 1.95 (s, 3, $OCOCH_3$), 2.10 (d, J = 15 Hz, 1, C-9β H), 2.15 (s, 3, $OCOCH_3$), 2.75–2.90 (m, 1, C-13β H), 3.43 (t, J = 3 Hz, 1, C-7β H), 3.47 (s, 3, OCH_3), 4.45 (dd, J = 3 and 9 Hz, 1, C-1α H), 4.96 (dd, J = 5 and 11 Hz, 1, C-15 H), 6.18 (d, J = 12 Hz, 1, C-11 H); exact mass spectrum calcd for $C_{24}H_{34}O_6$ $[M - CH_4O]^+$ 418.2357, found 418.2357.

Isomerization of 1β,11β-Diacetoxy-16β-methoxy-9β-picrasan-12-one (27b) to 1β,11β-Diacetoxy-16α-methoxy-9β-picrasan-12-one (27a). A solution of 7 mg (0.0155 mmol) of **27b** and 2.9 mg (0.0155 mmol, 1 equiv) of *p*-toluenesulfonic acid monohydrate in 0.5 mL of methanol was refluxed for 2 h. The mixture was diluted with ethyl acetate and washed successively with 5% aqueous sodium bicarbonate solution and brine. The organic layer was dried and chromatographed on silica gel with 1:4 ethyl acetate–hexane to give 6 mg of a separable 5:1 mixture of **27a** and **27b**, respectively, according to ^1H NMR spectroscopy.

1β,11β-Dihydroxy-16α-methoxy-9β-picrasan-12-one. To 11 mg (0.0244 mmol) of **27a** in 0.2 mL of anhydrous methanol was added 8.4 mg (0.061 mmol, 2.5 equiv) of anhydrous potassium carbonate. The mixture was stirred for 6 h at 25 °C, diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with 1:1 ethyl acetate–hexane to give 4.5 mg (51%) of 1β,11β-dihydroxy-16α-methoxy-9β-picrasan-12-one: IR ($CHCl_3$) 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 6 Hz, 3, C-4α CH_3), 1.10 (d, J = 8 Hz, 3, C-13 CH_3), 1.13 (s, 3, C-10β CH_3), 1.33 (s, 3, C-8β CH_3), 2.03 (d, J = 11 Hz, 1, C-9β H), 2.02–2.1 (m, 1, C-14 H), 3.00–3.14 (m, 1, C-13β H), 3.29 (s, 3, OCH_3), 3.69 (t, J = 3 Hz, 1, C-7β H), 3.76–4.00 (m, 3, C-1 and C-11 OH, C-1α H), 4.31 (d, J = 11 Hz, 1, C-11α H), 4.54 (t, J = 5 Hz, 1, C-16β H); exact mass spectrum calcd for $C_{21}H_{34}O_5$ 366.2408, found 366.2407.

12-Hydroxy-16α-methoxypicras-12-ene-1,11-dione. To a solution of 43 μL (0.612 mmol, 12 equiv) of dimethyl sulfoxide in 150 μL of dichloromethane was added 65 μL (0.459 mmol, 9 equiv) of trifluoroacetic anhydride at −78 °C. After 10 min, a solution of 1β,11β-dihydroxy-16α-methoxy-9β-picrasan-12-one (crude product from the saponification of 23 mg of **27a** according to the procedure described above) in 150 μL of dichloromethane was added. The solution was stirred for 30 min at −78 °C, and to this solution was added 142 μL (1.02 mmol, 20 equiv) of triethylamine. The mixture was allowed to warm to 25 °C, stirred for 5 min at 25 °C, and poured into water. The product was extracted with dichloromethane, washed with brine, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with 1:4 ethyl acetate–hexane to give 6 mg (33%) of 12-hydroxy-16α-methoxypicras-12-ene-1,11-dione: IR ($CHCl_3$) 1690, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 6 Hz, 3, C-4α CH_3), 1.14 (s, 3, C-8β CH_3), 1.28 (s, 3, C-10β CH_3), 1.81 (s, 3, C-13 CH_3), 3.32 (s, 3, OCH_3), 3.34 (s, 1, C-9α H), 3.63 (t, J = 3 Hz, 1, C-7β H), 4.44 (dd, J = 5 and 9 Hz, 1, C-16 H), 5.67 (s, 1, OH); exact mass spectrum calcd for $C_{21}H_{30}O_5$ 362.2095, found 362.2093.

12,16α-Dimethoxypicras-12-ene-1,11-dione (28). To 6 mg (0.0166 mmol) of 12-hydroxy-16α-methoxypicras-12-ene-1,11-dione in 103 μL of *N,N*-dimethylformamide was added 103 μL (1.66 mmol, 100 equiv) of iodomethane. The mixture was cooled to −20 °C, and 4 mg (0.166 mmol, 10 equiv) of sodium hydride was added. The mixture was stirred for 40 min at −20 °C and quenched with saturated ammonium chloride solution. The product was extracted with ethyl acetate, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated to afford 6 mg (97%) of **28**: IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6 Hz, 3, C-4α CH_3), 1.12 (s, 3, C-8β CH_3), 1.26 (s, 3, C-10β CH_3), 1.81 (s, 3, C-13 CH_3), 2.52–2.84 (m, 2, C-2 CH_2), 3.30 (s, 1, C-9α H), 3.30 (s, 3, C-16 OCH_3), 3.54 (s, 3, C-12 OCH_3), 3.61 (t, J = 3 Hz, 1, C-7β H), 4.42 (dd, J = 5 and 9 Hz, 1, C-16β H); exact mass spectrum calcd for $C_{22}H_{32}O_5$ 376.2251, found 376.2250.

(+)-2-Deoxypicrasin B (29). A solution of 4.8 mg (0.0127 mmol) of **28** in 1.4 mL of 60% aqueous acetic acid was refluxed for 25 min under a nitrogen atmosphere. The solvent was evaporated under reduced pressure to afford 4.6 mg of δ-lactol, which was used in the next reaction without purification. The major C-16 diastereomer of the δ-lactol had the following spectral data: IR ($CHCl_3$) 3595, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 5 Hz, 3, C-4α CH_3), 1.12 (s, 3, C-8β CH_3), 1.28 (s, 3, C-10β CH_3), 1.81 (s, 3, C-13 CH_3), 2.39–2.48 (m, 1, C-14 CH), 3.30 (s, 1, C-9α H), 3.53 (s, 3, OCH_3), 3.78 (t, J = 3 Hz, 1, C-7β H), 4.95 (dd, J = 5 and 9 Hz, 1, C-16 H); exact mass spectrum calcd for $C_{21}H_{30}O_5$ 362.2095, found 362.2093.

To a solution of crude δ-lactol in 1.5 mL of anhydrous benzene was added 635 mg (0.635 mmol, 50 equiv) of silver carbonate on Celite.[25] The suspension was refluxed for 1.5 h under a nitrogen atmosphere. The mixture was filtered and concentrated to give the crude product, which was chromatographed on silica gel with 1:10 ethyl acetate–hexane to give 2.7 mg (59%) of **29**: $[\alpha]_D$ = +10.5° (c 9.5 × 10^{-4}, $CHCl_3$); IR ($CHCl_3$) 1725, 1703, 1682, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, J = 6 Hz, 3, C-4α CH_3), 1.20 (s, 3, C-8β CH_3), 1.49 (s, 3, C-10β CH_3), 1.90 (s, 3, C-13 CH_3), 3.22 (s, 1, C-9α H), 3.66 (s, 3, OCH_3), 4.27 (t, J = 3 Hz, 1, C-7β H); exact mass spectrum calcd for $C_{21}H_{28}O_5$ 360.1938, found 360.1940.

(−)-2-Bromo-2-deoxypicrasin B (30). To 30 mg (0.083 mmol) of **29** in 5 mL of methanol was added 186 mg (0.83 mmol) of cupric bromide at 25 °C under a nitrogen atmosphere. The mixture was refluxed for 15 h. After cooling, the product was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel with 3:1 ethyl acetate–hexane to afford 15.9 mg (44%) of **30**: $[\alpha]_D$ −14.3° (c 3.9 × 10^{-3}, $CHCl_3$); IR (TF) 1735, 1695, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6 Hz, 3, C-4α CH_3), 1.21 (s, 3, C-8β CH_3), 1.51 (s, 3, C-10β CH_3), 1.91 (s, 3, C-13 CH_3), 3.01 (dd, J = 6 and 18 Hz, 1, C-15β H), 3.30 (s, 1, C-9α H), 3.65 (s, 3, C-12 OCH_3), 4.28 (t, J = 3 Hz, 1, C-7β H), 5.36 (dd, J = 6 and 13 Hz, 1, C-2β H); exact mass spectrum calcd for $C_{21}H_{27}Br^{79}O_5$ 438.1043, found 438.1042.

(−)-Picrasin B Acetate (31). To 15 mg (0.034 mmol) of **30** in 500 μL of anhydrous acetone was added 182 mg (1.36 mmol) of tetramethylammonium acetate at 25 °C under a nitrogen atmosphere. The mixture was refluxed for 5 h. After cooling, the product was diluted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The product was chromatographed on silica gel in 3:1 ethyl acetate–hexane to afford 6.9 mg (49%) of **31**: $[\alpha]_D$ = −36.5° (c 8.3 × 10^{-3}, $CHCl_3$); IR (TF) 1720, 1675, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 6 Hz, 3, C-4α CH_3), 1.21 (s, 3, C-10β CH_3), 1.52 (s, 3, C-8β CH_3), 1.90 (s, 3, C-13 CH_3), 2.14 (s, 3, $OCOCH_3$), 3.02 (dd, J = 5 and 20 Hz, 1, C-15β H), 3.21 (s, 1, C-9α H), 3.65 (s, 3, OCH_3), 4.29 (t, J = 3 Hz, 1, C-7β H), 5.89 (dd, J = 7 and 14 Hz, 1, C-2β H); exact mass spectrum calcd for $C_{23}H_{30}O_7$ 418.1993, found 418.1992.

(+)-Picrasin B (1). To 15 mg (0.036 mmol) of **31** in 300 μL of anhydrous methanol at 25 °C under nitrogen atmosphere was added 5.4 mg (0.039 mmol, 1.1 equiv) of potassium carbonate. The mixture was stirred for 30 min at 25 °C. The product was diluted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel with 3:1 ethyl acetate–hexane to afford 10.2 mg (76%) of **1**: $[\alpha]_D$ = +2.1° (c 6.55 × 10^{-3}, MeOH); IR (TF) 3450, 1730, 1700, 1670, 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6 Hz, 3, C-4α CH_3), 1.22 (s, 3, C-8β CH_3), 1.47 (s, 3, C-10β CH_3), 1.92 (s, 3, C-13 CH_3), 3.01 (dd, J = 6 and 18 Hz, 1, C-15β H), 3.25 (s, 1, C-9α H), 3.50 (d, J = 4 Hz, 1, OH), 3.67 (s, 3, OCH_3), 4.32 (t, J = 3 Hz, 1, C-7β H), 4.78–4.92 (m, 1, C-2β H); exact mass spectrum calcd for $C_{21}H_{28}O_6$ 376.1887, found 376.1888.

Picrasin B (1) from (+)-Quassin (12). To 299 mg (0.77 mmol) of quassin (**12**) (Pfaltz and Bauer, purified) in 10 mL of acetonitrile at 25 °C under a nitrogen atmosphere was added 404 mg (2.7 mmol) of sodium iodide followed by 342 μL (2.7 mmol) of chlorotrimethylsilane. The mixture was stirred for 18 h and quenched by the addition of 5% aqueous sodium thiosulfate solution. The mixture was diluted with ethyl acetate and washed successively with water and brine. The organic layer was dried and chromatographed on silica gel with 2:1 ethyl acetate–hexane to afford 120 mg (42%) of **1**, having all spectral data in accord with published values, and 28 mg (9%) of 2-methoxy-2-deoxypicrasin B[12] (**45**).

(−)-Picrasin B Acetate (31) from (+)-Picrasin B (1). The procedure described for the preparation of **20** was repeated using 164 mg (0.436 mmol) of **1**, 2.91 mL (30.8 mmol) of acetic anhydride, and 6.5 mL of anhydrous pyridine to afford, after chromatography on silica gel with 1:1 ethyl acetate–hexane, 141 mg (77%) of **31**, which was identical in all respects with the product from **3**.

(+)-2-Deoxypicrasin B (29) from (−)-Picrasin B Acetate (31). To a solution of 107 mg (0.256 mmol) of **31** in 5 mL of glacial acetic acid was added 2.0 g (30.7 mmol) of zinc dust.[28] The suspension was refluxed for 3 h. The mixture was filtered and concentrated to give the crude product, which was chromatographed on silica gel with 2:1 ethyl acetate–hexane to afford 72 mg (78%) of **29**, which was identical in all respects with the product from **3**.

(+)-Δ²-Picrasin B (11) from Picrasin B (1). The procedure described for the preparation of 12-hydroxy-16α-methoxypicras-12-ene-1,11-dione was repeated using 33 mg (0.0877 mmol) of **1**, 75 μL (1.05 mmol, 12 equiv) of dimethyl sulfoxide, 111 μL (0.789 mmol, 9 equiv) of trifluoroacetic anhydride, and 244 μL (1.75 mmol, 20 equiv) of triethylamine to afford, after chromatography on silica gel with 1:1 ethyl acetate–hexane, 5.8 mg (18%) of **1** and 20.3 mg (62%) of **11**: $[\alpha]_D$ = +30.6° (c 3.6 × 10^{-3} g/mL, $CHCl_3$); IR (TF) 3420, 1720, 1683, 1675, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (d, J = 7 Hz, 3, C-4α CH_3), 1.22 (s, 3, C-8β CH_3), 1.60 (s, 3, C-10β CH_3), 1.90 (s, 3, C-13 CH_3), 2.92 (s, 1, C-9α H), 3.02 (dd, J = 6 Hz and 18 Hz, 1, C-15β H), 3.70 (s, 3, OCH_3), 4.30 (t, J = 2 Hz, 1, C-7β H), 5.63 (s, 1, OH), 5.74 (d, J = 2 Hz, 1, C-3 H); exact mass spectrum calcd for $C_{21}H_{26}O_6$ 374.1730, found 374.1729.

(+)-Quassin (12) from (+)-Δ²-Picrasin B (11). The procedure described for the preparation of **28** was repeated using 6 mg (0.016 mmol) of **11**, 100 μL (1.6 mmol, 100 equiv) of iodomethane, 3.8 mg (0.16 mmol, 10 equiv) of sodium hydride, and 100 μL of *N,N*-dimethylformamide to afford, after chromatography on silica gel with 2:1 ethyl acetate–hexane, 5.3 mg (85%) of **12** that was identical with the purified commerical material purchased from Pflatz and Bauer.

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Registry No. 1, 26121-56-2; **6a**, 123834-99-1; **6b**, 123834-68-4; **7a**, 123835-01-8; **7a** (*O*-demethyl deriv), 123835-00-7; **7b**, 123834-69-5; **7b** (*O*-demethyl deriv), 123834-67-3; **8**, 123834-70-8; **11**, 26121-57-3; **12**, 76-78-8; **15**, 123929-85-1; **16**, 123834-74-2; **17**, 123834-75-3; **18**, 123834-76-4; **19**, 123834-77-5; **20**, 123834-78-6; **21**, 123834-79-7; **22**, 123834-80-0; **23**, 123857-40-9; **24a**, 123834-81-1; **24b**, 123834-72-0; **25a**, 123834-82-2; **25b**, 123834-98-0; **26a**, 123834-83-3; **26b**, 123834-73-1; **27a**, 123834-84-4; **27a** (deacetyl deriv), 123834-65-1; **27b**, 123857-39-6; **28**, 123834-85-5; **28** (12-

hydroxy deriv), 123834-66-2; **29**, 123834-86-6; **30**, 123834-87-7; **31**, 30315-04-9; **32**, 123834-88-8; **33**, 123834-89-9; **34**, 123834-90-2; **35**, 123834-91-3; **36**, 123834-92-4; **37**, 123834-93-5; **38**, 123834-89-9; **39**, 123834-94-6; **40**, 123834-88-8; **41**, 123834-95-7; **41** (20-alcohol), 111324-69-7; **42**, 123835-02-9; **43**, 123834-96-8; **44**, 123857-41-0; **45**, 123834-97-9; (*E*)-CH_2=C(OTMS)C(CH_3)=$CHOCH_3$, 54125-02-9; (±)-$BrCH_2CH(OMe)Br$, 66556-47-6; 20-(benzoyloxy)-1β-*tert*-butyldimethylsilyloxy-18-ethoxy-18-nor-9β-picrasan-12-one, 123929-84-0; 20-(benzoyloxy)-16-ethoxy-1β-hydroxy-18-nor-9β-picrasan-12-one, 123834-71-9.

Supplementary Material Available: Experimental details for the preparation of compounds **7**, **8**, **32–41**, and **43** (9 pages). Ordering information is given on any current masthead page.

Synthesis and Application of Tertiary Allylic Nitro Compounds

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A new procedure was developed for the synthesis of tertiary allylic nitro compounds. Secondary nitroalkanes (comprising nitrocyclohexane, 2-nitroheptane, 4-nitro-1-pentene, and 2-nitropropane) were treated with 1.5 equiv of electron-deficient acetylenes (including methyl propiolate, dimethyl acetylenedicarboxylate, and 3-butyn-2-one) to give the corresponding tertiary allylic nitro adducts in 62–90% yields. These reactions required 5.0 equiv of potassium fluoride as the base, 1.0 equiv of tetra-*n*-butylammonium chloride as the phase-transfer catalyst, and dimethyl sulfoxide as the solvent. Tertiary allylic nitro compounds were also synthesized by the double Michael addition of 1 equiv of primary nitroalkanes to 2 equiv of electron-deficient acetylenes in the presence of potassium fluoride, tetra-*n*-butylammonium chloride, and dimethyl sulfoxide. Thus, nitroethane and methyl 4-nitrobutyrate (**5**) individually reacted with 3.0–3.5 equiv of methyl propiolate to give dimethyl 3-methyl-3-nitro-1,4-pentadiene-1,5-dicarboxylate (**6**) in 75% yield and dimethyl 3-[2-(methoxycarbonyl)ethyl]-3-nitro-1,4-pentadiene-1,5-dicarboxylate (**7**) in 53% yield, respectively. Furthermore, the double Michael addition proceeded well when two different Michael acceptors were added sequentially: acetylenes followed by electron-deficient alkenes. Reaction of nitroethane with 1.0 equiv of methyl propiolate or 3-butyn-2-one and then with 2.0 equiv of methyl vinyl ketone afforded (*E*)-methyl 4-methyl-4-nitro-7-oxo-2-octenoate (**8**) in 60% yield and (*E*)-5-methyl-5-nitro-3-nonene-2,8-dione (**9**) in 52% yield, respectively. Alkenes containing an electron-withdrawing substituent and an alkyl group at the α- or the β-position were also employed in the double Michael addition; however, they must be used as the first Michael acceptor. Thus, nitroethane reacted with 1.0 equiv of ethyl methacrylate and then with 1.5 equiv of methyl propiolate to give (*E*)-methyl 6-(ethoxycarbonyl)-4-methyl-4-nitro-2-heptenoate (**10**) in 41% yield. In a similar reaction involving 2-cyclohexen-1-one, instead of ethyl methacrylate, a mixture of (*E*)- and (*Z*)-methyl 4-nitro-4-(3-oxocyclohexyl)-2-pentenoate (**11**) was obtained in 50% yield. The newly developed double Michael addition was used as the key step in a total synthesis of (±)-norsolanadione, a biologically active terpenoid.

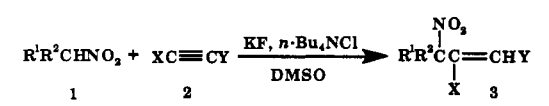
Introduction

The nitro group in organic compounds plays an important role in carbon–carbon bond formation and functionality transformation.[1,2] In the latter category, tertiary allylic nitro compounds are versatile synthetic intermediates because they can be easily transformed to different classes of organic materials. The tertiary allylic nitro group can be readily replaced by nucleophiles, such as amines,[3] enolates,[3-5] lithium dialkylcuprates,[6] sulfinates,[7] and thiolates.[7] Also, the nitro group can be reduced to an amine[2] or be replaced by a hydride.[8] The applicability of tertiary allylic nitro compounds in synthesis is nevertheless limited because only a few *general* methods exist for their preparation. We therefore sought a new, efficient method for the synthesis of tertiary allylic nitro compounds.

Tanikaga et al. reported a procedure for the preparation of tertiary allylic nitro compounds from nitroalkanes and phenyl vinyl sulfoxide.[9] This procedure requires two steps and high reaction temperature (180 °C). Ono, Tamura, and co-workers developed another method, in which nitroalkenes react with aldehydes or electron-deficient olefins.[10,11] Preparation of the starting material nitroalkanes usually requires two steps or more.[12]

We report herein that the Michael addition of secondary nitroalkanes to electron-deficient acetylenes gave good to excellent yields of tertiary allylic nitro compounds. This class of compounds also can be obtained by an unprecedented double Michael addition of primary nitroalkanes

Scheme I



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