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Registry No. 1, 103-81-1; **2**, 89789-99-1; **3**, 89790-00-1; **4**, 1125-70-8; **5**, 10255-95-5; **6**, 64-10-8; **7**, 10268-06-1; **8**, 58357-84-9; **9**, 20101-92-2; **10**, 332-29-6; **11**, 74860-13-2; **12**, 84863-81-0; **13**, 6343-93-7; **14**, 40784-91-6; **15**, 89790-01-2; **16**, 89790-02-3; **17**, 3413-59-0; **18**, 89790-03-4; **19**, 14442-83-2; **20**, 5100-05-0; **21**, 84199-13-3; **22**, 89790-04-5; **23**, 89790-05-6; **24**, 19026-73-4; **25**, 102-93-2; **26**, 621-79-4; **27**, 621-88-5; **28**, 1199-98-0; **29**, 89790-06-7; **30**, 89790-07-8; **31**, 89790-08-9; **32**, 6343-54-0; **33**, 86386-69-8; **34**, 87578-63-0; **35**, 89790-09-0; **36**, 89790-10-3; **37**, 89790-11-4; **38**, 89790-12-5; **39**, 89790-13-6; **40**, 588-46-5; **41**, 7387-69-1; **42**, 17105-71-4; **43**, 6224-99-3; **44**, 89790-14-7; **45**, 61382-93-2; **46**, 89790-15-8; **47**, 629-54-9; **48**, 89790-17-0; **49**, 89790-18-1; **50**, 89790-19-2; **51**, 89790-20-5; **52**, 89790-21-6; **53**, 89790-22-7; **54**, 87053-07-4; **55**, 89790-23-8; **56**, 89790-24-9; **57**, 89790-25-0; phenylacetonitrile, 140-29-4; *p*-pentoxyphenylacetonitrile, 50690-55-6; 3-phenylpropionic acid, 501-52-0; *p*-butoxyphenylacetic acid, 4547-57-3; methyl *p*-butoxyphenylacetate, 29056-06-2; benzylamine, 100-46-9; formic acid, 64-18-6; acetic anhydride, 108-24-7; trifluoroacetic anhydride, 407-25-0; *p*-hydroxyphenylacetonitrile, 14191-95-8; *p*-hydroxyphenylacetic acid, 156-38-7; 3-(*p*-butoxyphenyl)propanoic acid, 3243-41-2; *m*-hydroxybenzylic alcohol, 621-37-4; methyl 8-hydroxyoctanoate, 20257-95-8; *p*-hydroxybenzaldehyde, 123-08-0; *p*-butoxybenzaldehyde, 5736-88-9; cyanomethyltriphenylphosphonium chloride, 4336-70-3; *p*-butoxycinnamonitrile, 89790-26-1; 3-(*p*-butoxyphenyl)propionitrile, 89790-27-2; 11-aminoundecanoic acid, 2432-99-7; *N*-formyl-11-aminoundecanoic acid, 3611-31-2; methyl-11-aminoundecanoic acid, 28691-27-2; *p*-butoxybenzonitrile, 38746-93-9; glycine, 56-40-6; *N*-formylglycine, 2491-15-8; propylamine, 107-10-8; 1-bromopentane, 110-53-2; *n*-pentyltriphenylphosphonium bromide, 21406-61-1; 4-cyanobenzaldehyde, 105-07-7; 1-(*p*-cyanophenyl)hexene-1, 89790-28-3; 1-(*p*-cyanophenyl)hexane, 29147-95-3; *p*-arbutin, 497-76-7; iodoacetamide, 144-48-9; *m*-butoxybenzyl alcohol, 30609-21-3; *m*-butoxybenzoyl chloride, 89790-29-4; *m*-butoxyphenylacetnitrile, 74205-57-5; methyl 8-hydroxyoctanoate tosylate, 89790-30-7; *p*-(7-methoxycarbonylheptamethyleneoxy)phenylacetamide, 89790-31-8; (triphenylphosphoranylidene)acetonitrile, 16640-68-9; triphenylphosphine, 603-35-0; chloroacetonitrile, 107-14-2; methyl 11-guanidinoundecanoate hemisulfate, 89790-33-0; alcohol dehydrogenase, 9031-72-5.

Communications to the Editor

General Synthesis of Pentacyclic Quassinoids

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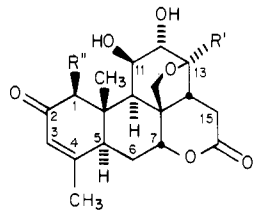
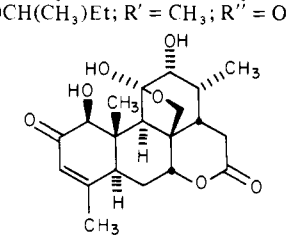
The family of bitter principles known as quassinoids includes compounds displaying antileukemic, antineoplastic, antimalarial, and even insecticidal and antifeedant properties.[1] Among these, only pentacyclic quassinoids, which possess A-ring enone functionality and a bridging ether to C11 or C13 (e.g. **1**–**4**), are of



1, R = COCH=C(CH_3)-*i*-Pr; R′ = CO_2CH_3; R″ = H
2, R = COC(CH_3)(OAc)Et; R′ = CH_3; R″ = OH
3, R = COCH(CH_3)Et; R′ = CH_3; R″ = OH



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medicinal interest. Here we describe a series of stereoselective annelations as well as a novel isomerization of C13- to C11-bridged intermediates, which for the first time permits access to both main classes of pentacyclic quassinoids.[2]

Much of the carbon skeleton was assembled in a single conjugate addition–enolate trapping using *trans*-1-iodo-3-(benzyloxy)-1-pentene (**5**)[3] and 4-prenyl-3-methyl-2-cyclohexenone (**6**) (Scheme I).[4] Modification of Noyori's organocopper-based procedure[5] generated a reactive lithium enolate suitable for in situ alkylation. Thus **5** was metalated (*n*-BuLi, 1.2 equiv, Et_2O) then treated with CuI–Bu_3P (2 equiv) at −70 °C. After addition of **6** (1 equiv), the mixture was warmed to −35 °C (1.5 h) and recooled, and more *n*-BuLi (1.2 equiv) was added to transform the obligatory Cu(I) enolate to $(n\text{-BuCu})_x$ and a lithium enolate. Subsequent addition of $(EtO)_2POCl$–Et_3N (4 equiv) furnished triene **7** as a colorless oil in 87% yield (20-g scale).[6] This improved coupling should find widespread use when both the nucleophile and electrophile must not be wasted. The stereochemistry shown in **7**, anticipated from related cuprate additions,[7] was later confirmed by X-ray diffraction analysis.[8]

Reductive cleavage of **7** (Li, NH_3, *t*-BuOH) then oxidation of **8** afforded enone **9** (75%). Stereoselective conjugate addition of ethyl cyanoacetate to **9** furnished **10** (55%), establishing the correct configuration at C9 (vide infra) for the quassinoids. Ozonolysis and cyclization of **10** (Me_2S–$NaHCO_3$) formed alcohol **11**, as judged by the C7 methine resonance in its acetate ester **12** (δ 5.36, J = 11.1, 4.8 Hz). Cyclization of **11** (LiOEt, EtOH, room tem-

(1) For a review, see: Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101.

(2) For leading references to synthetic efforts at quassinoid total synthesis, see: Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601.

(3) Prepared from *trans*-1-chloro-1-penten-3-one according to the procedure of: Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

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(6) Satisfactory IR, NMR, and mass spectral data have been obtained for all new substances described.

(7) (a) Wege, P. M.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 3144. (b) Ziegler, F. E.; Reid, G. R.; Studt, W. L.; Wender, P. A. *Ibid.* **1977**, *42*, 1991.

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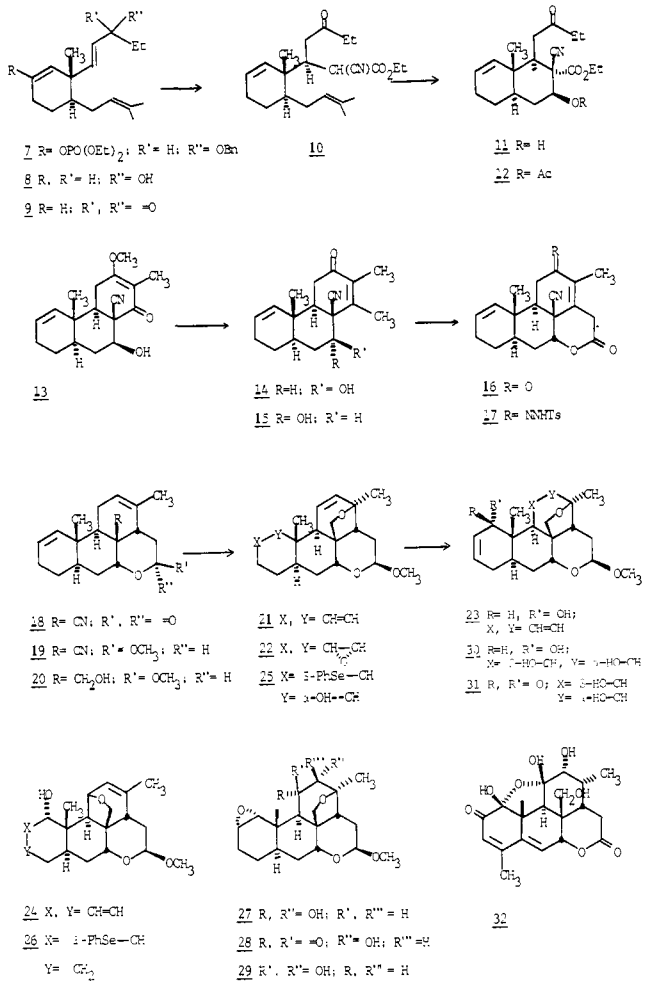
Scheme I



perature, 10 min) led to ketone **13** after enol etherification [$HC(OCH_3)_3$, *p*-TsOH, room temperature; 83% from **10**].

Methyllithium addition–hydrolysis converted **13** to **14**. This enone was epimerized upon Jones oxidation, DIBAL reduction, and MnO_2 reoxidation to furnish **15** (52% overall from **13**). Besides the establishment of the axial C9 configuration in both **14** and **15** from C9–C11 coupling constants, 300-MHz ^1H NMR spectroscopy also verified the C7 stereochemical assignments, since the axial C7 hydroxyl in **15** caused a 0.3 ppm downfield shift in its C9 hydrogen resonance (relative to **14**). Treatment of **15** with 1,1′-carbonyldiimidazole (THF, reflux) then with KH (12 equiv, room temperature) afforded tetracyclic lactone **16**, mp 242–244 °C, in over 90% yield.

Hydride reagents reduced the C12 ketone of **16** stereoselectively from the less hindered α-face. This preference was exploited to establish the correct configuration at C14 and complete the pentacyclic system. Thus, tosylhydrazone **17** underwent reductive rearrangement ($NaBH_3CN$–HOAc, 68 °C)[9] to a single diene **18** (55% from **16**). By stepwise DIBAL reductions, cyanolactone **18** furnished acetal **19** then alcohol **20**. Selenocyclization of **20** (PhSeCl, CH_2Cl_2, 3 h)[10] followed by oxidative elimination of PhSeOH furnished diene **21** in 62% yield. Long-range W coupling between the C12 and C14 hydrogens in **21** verified the diaxial fusion of ring D to the carbocyclic system.

Regio- and stereoselective monoepoxidation of **21** furnished **22**, which rearranged to allylic alcohol **23** with *n*-butyllithium or lithium diisopropylamide (LDA). Upon standing at room temperature or during prolonged exposure to silica gel, **23** isomerized completely to the pentacyclic structure **24**. While diene **21** showed no tendency to rearrange, hydroxy selenide **25** also isomerized quantitatively to C11-bridged **26**, thus implicating some anchimeric assistance by the C1 α-hydroxyl group. Such participation seems plausible in view of the recently reported quassinoid hemiketal karinolide **32**.[11] *With this serendipitous discovery, both structural classes of ring-C bridging ethers now become synthetically accessible.* Progress toward the synthesis of a fully functionalized C13-bridged quassinoid is documented below.

Osmylation of alkene **22** furnished *cis*-diol **27** (62%), which was further oxidized selectively to hydroxy ketone **28** by using pyridinium dichromate.[12] In keeping with the model study published by Fuchs,[13] **28** could be reduced by using Bu_4NBH_4 (4 equiv, EtOAc, room temperature, 7 h) to afford crystalline trans-diaxial diol **29** exclusively (40% from **27**). Epoxide **29** was smoothly isomerized (PhSeNa, H_2O_2) to **30**. Selective oxidation of the allylic hydroxyl produced enone **31**, a potentially bioactive quassinoid whose pharmacological properties are presently under investigation.

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Registry No. 7, 89827-65-6; **8**, 89827-66-7; (±)-**9**, 89827-67-8; **10**, 89827-68-9; (±)-**11**, 89827-69-0; (±)-**13**, 89827-70-3; (±)-**14**, 89827-71-4; (±)-**15**, 89827-72-5; (±)-**16**, 89827-73-6; (±)-**17**, 89848-04-4; (±)-**18**, 89827-74-7; (±)-**20**, 89827-75-8; (±)-**21**, 89827-76-9; (±)-**22**, 89827-77-0; (±)-**23**, 89827-79-2; (±)-**24**, 89848-05-5; (±)-**25**, 89827-78-1; (±)-**26**, 89848-06-6; (±)-**27**, 89827-82-7; (±)-**28**, 89827-83-8; (±)-**29**, 89827-84-9; (±)-**30**, 89827-80-5; (±)-**31**, 89827-81-6; ethyl cyanoacetate, 105-56-6.

Supplementary Material Available: Physical properties, NMR (^1H and ^{13}C), and IR data of all new compounds described (7 pages). Ordering information is given on any current masthead page.

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(*E*)-β-(Fluoromethylene)-*m*-tyrosine: A Substrate for Aromatic L-Amino Acid Decarboxylase Liberating an Enzyme-Activated Irreversible Inhibitor of Monoamine Oxidase

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The concept of enzyme-activated irreversible inhibition has proven to be extremely fruitful for the design of highly specific inhibitors of selected target enzymes.[1] For the therapeutic application of enzyme inhibitors, however, it is often desirable to achieve site specificity in addition to target enzyme specificity. An example where such dual specificity would be advantageous is the inhibition of monoamine oxidase[2] (MAO; EC 1.4.3.4). Although inhibitors of MAO[3] are effective antidepressants,[2a] their

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