

Acknowledgment. We are indebted to Professor C. I. Bränden and Dr. H. Eklund (Uppsala, Sweden) for providing us coordinates and extensive structural information, and all facilities in using the Graphic Display. Our thanks go to Professor H. Dutler (Basel, Switzerland) and C. I. Bränden for the diamond lattice adapted to the substrate site of the enzyme. This work was supported by grants from the Institute de Recherches Scientifiques Economiques et Sociales sur les Boissons (I.R.E.B.), from the Fondation pour la Recherche Médicale Française, and from the P.I.R.M.E.D. (ASP-CNRS No. 2280).

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*-pentoxyphenylacetoneitrile, 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*-hydroxyphenylacetoneitrile, 14191-95-8; *p*-hydroxyphenylacetic acid, 156-38-7; 3-(*p*-butoxyphenyl)propanoic acid, 3243-41-2; *m*-hydroxybenzyl 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*-butoxycinnamoneitrile, 89790-26-1; 3-(*p*-butoxyphenyl)propionitrile, 89790-27-2; 11-aminoundecanoic acid, 2432-99-7; *N*-formyl-11-amino-undecanoic 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*-butoxyphenylacetoneitrile, 74205-57-5; methyl 8-hydroxyoctanoate tosylate, 89790-30-7; *p*-(7-methoxycarbonyl)heptamethyleneoxyphenylacetamide, 89790-31-8; (triphenylphosphoranylidene)acetoneitrile, 16640-68-9; triphenylphosphine, 603-35-0; chloroacetoneitrile, 107-14-2; methyl 11-guanidinoundecanoate hemisulfate, 89790-33-0; alcohol dehydrogenase, 9031-72-5.

Communications to the Editor

General Synthesis of Pentacyclic Quassinoids

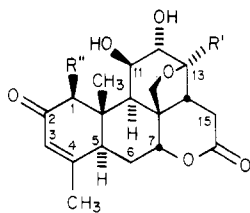
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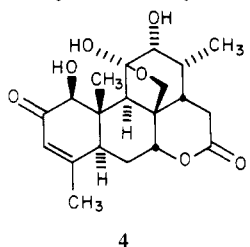
Received January 4, 1984

Revised Manuscript Received March 12, 1984

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(CH₃)-*i*-Pr; R' = CO₂CH₃; R'' = H
2, R = COC(CH₃)(OAc)Et; R' = CH₃; R'' = OH
3, R = COCH(CH₃)Et; R' = CH₃; 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-(benzyl-oxy)-1-pentene (5)³ and 4-prenyl-3-methyl-2-cyclohexenone (6) (Scheme I).⁴ Modification of Noyori's organocopper-based procedure⁵ generated a reactive lithium enolate suitable for in situ alkylation. Thus 5 was metalated (*n*-BuLi, 1.2 equiv, Et₂O) then treated with CuI-Bu₃P (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*-BuCu)_x and a lithium enolate. Subsequent addition of (EtO)₂POCl-Et₃N (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, NH₃, *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 (Me₂S-NaHCO₃) 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-

(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.

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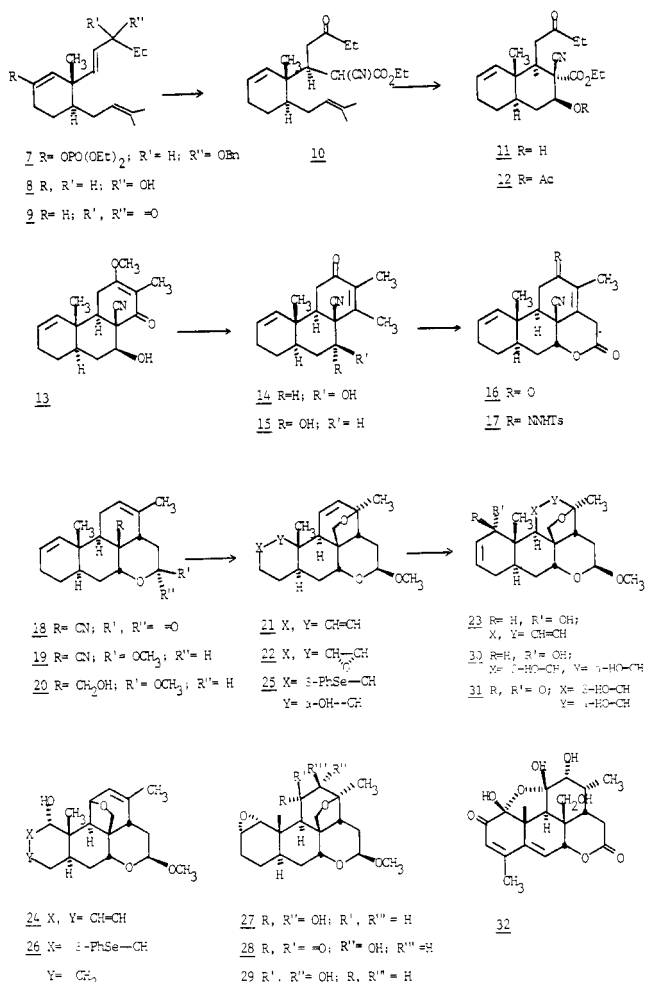
(6) Satisfactory IR, NMR, and mass spectral data have been obtained for all new substances described.

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

Scheme 1



perature, 10 min) led to ketone **13** after enol etherification [HC(OCH₃)₃, *p*-TsOH, room temperature; 83% from **10**].

Methylolithium addition-hydrolysis converted **13** to **14**. This enone was epimerized upon Jones oxidation, DIBAL reduction, and MnO₂ 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 (NaBH₃CN-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, CH₂Cl₂, 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 Bu₄NBH₄ (4 equiv, EtOAc, room temperature, 7 h) to afford crystalline trans-diaxial diol **29** exclusively (40% from **27**). Epoxide **29** was smoothly isomerized (PhSeNa, H₂O₂) to **30**. Selective oxidation of the allylic hydroxyl produced enone **31**, a potentially bioactive quassinoid whose pharmacological properties are presently under investigation.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for generous financial assistance. Support of the Cornell Nuclear Magnetic Resonance Facility by the National Science Foundation (CHE 7904825; PCM 8018643) is gratefully acknowledged.

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 ¹³C), 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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Received December 7, 1983

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 oxidase² (MAO; EC 1.4.3.4). Although inhibitors of MAO³ are effective antidepressants,^{2a} their

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