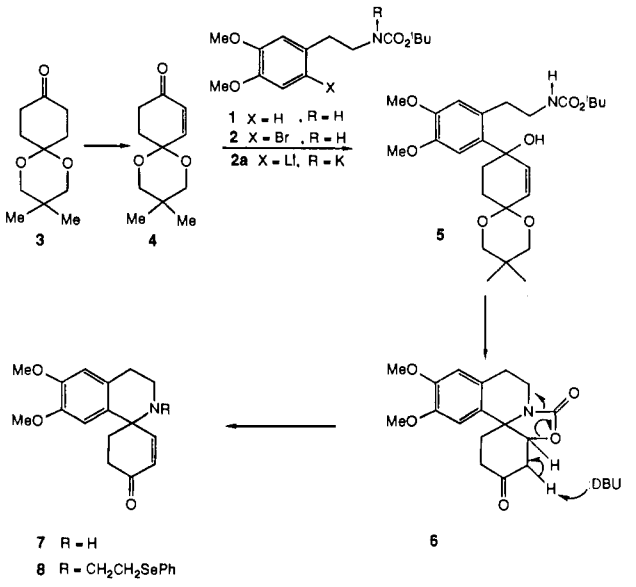
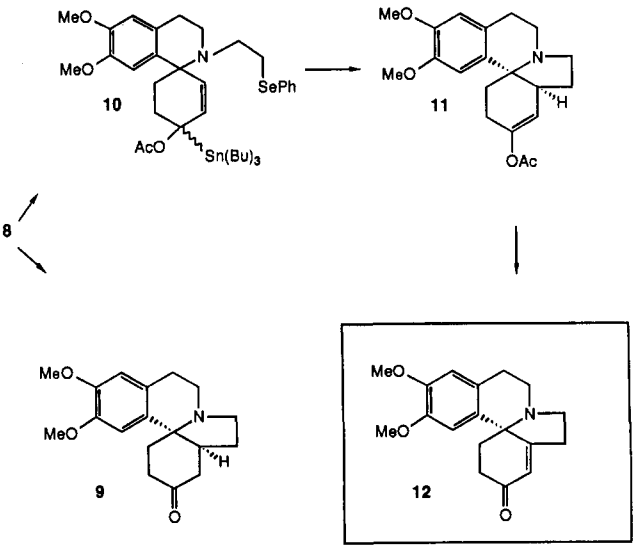


function[9a] in a vicinal relationship to the radical species. In light of the Tsuda work,[3] the synthesis of compound **9** constituted a formal total synthesis of **12**. The reduction to practice of the synthetic logic implied in eq 2 started with treatment of compound **8** with tri-*n*-butyllithiostannane[17] (Et_2O, −78 °C). Following extractive isolation, the resultant hydroxystannane was immediately acetylated with acetic anhydride (DMAP, CH_2Cl_2, Et_3N) to afford an 83% yield of ca. a 1:1 mixture of stereoisomers **10**. Happily, treatment of mixture **10** with $(n\text{-Bu})_3SnH$ in the presence of catalytic AIBN (5–10 mol %) afforded a 65% yield of a single stereoisomer formulated as **11**.[11,18] Advantage was now taken of the site-specific enol acetate. A three-step sequence [(i) MeLi–THF; (ii) PhSeCl, −78 °C; (iii) $NaIO_4$, aqueous THF) afforded a 64% yield of crystalline **12**, mp 105–108 °C, lit.[3] mp 101–102 °C. The NMR (500 MHz) and infrared spectra of synthetic **12**, as well as its chromatographic mobility, are identical with those of a reference sample provided by Professor Tsuda.



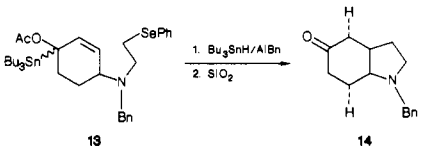
The work described herein suggests a high susceptibility for α-oxygenated, α-stannylated allylic systems to undergo free radical attack at the γ-carbon. In the case shown above, the radical source was tethered to the allylic residue by a nitrogen atom attached to the δ-carbon.[19] Other permutations for the tethering, as well as other variations in the nature of the attacking radical, might find extension to both heterocyclic and alicyclic synthesis. Such possibilities will be receiving continuing attention in our laboratories.

Acknowledgment. This work was supported by PHS Grant HL 25848. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. A PHS Postdoctoral Fellowship (Grant 5 F32 CA07752) to J.S.P. is gratefully acknowledged. We thank Professor Yoshisuke Tsuda of Kanazawa University for providing reference materials.

(17) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(18) The stereochemistry of the C5–C6 ring junction (erythrina numbering) of enol acetate **11** was based on ^1H NMR (500 MHz) experiments. The *J* value for the C1 vinyl proton equals 3.6 Hz. Thus, the C6 proton is equatorial and th C5–C6 ring junction is cis.

(19) That the additional rigidity imposed by the spiro tethering and the benzo linkage is not a sine qua non for the success of the reaction is suggested by the smooth transformation of the mixture cyclohexenyl epimers **13** to *cis*-*N*-benzyloctahydro-6-oxoindole (**14**).



Simple Synthetic Route to the Limonoid System

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Received September 26, 1986

Since the elucidation of the structure of limonin in 1960,[1] a large number of naturally occurring substances in this family, the limonoids,[2] have been isolated and characterized structurally. Despite the widespread occurrence of the limonoids (and further metabolic products such as the quassins) in nature and their interesting biological properties, the total synthesis of these compounds has remained an unsolved problem. We now report the first synthesis of the limonoid system by a simple route which is nonetheless sufficiently versatile to provide access to many limonoids.

The enol phosphate **1** was prepared in one flask in 80% yield by reaction of farnesyl bromide at 0 °C in tetrahydrofuran (THF) with the sodio and lithio derivative of methyl acetoacetate (1.2 equiv, 2 h), cooling to −78 °C, and further reaction with diethyl chlorophosphate (−78 °C for 20 min, −20 °C for 2 h).[3,4a] Slow addition of **1** (over 1.5 h) in dry nitromethane solution (0.1 M) to a solution of mercuric trifluoroacetate (0.08 M in nitromethane) at −22 °C and further reaction for 1 h at −22 °C afforded, after stirring with aqueous sodium chloride and isolation,[4a] tricyclic keto ester **2** (27–30% yield) as a crystalline solid, mp 201–202 °C.[5] Replacement of mercury by phenylseleno[11] was accomplished by treatment with diphenyl diselenide in methylene chloride solution at 23 °C with irradiation by a sunlamp (20 min), and the resulting selenide[4b] was converted to olefin **3**[4b] (70% overall) by oxidation with *m*-chloroperbenzoic acid at −78 °C in methylene chloride and then warming (in the presence of dimethyl sulfide and triethylamine) at 45 °C for 20 h. Keto ester **3** was transformed into the enol ester **4** (sodium hydride in THF at 23 °C for 3 h followed

(1) Arigoni, D.; Barton, D. H. R.; Caglioti, L.; Corey, E. J.; Sukh Dev; Ferrini, P. G.; Glazier, E. R.; Jeger, O.; Melera, A.; Pradhan, S. K.; Schaffner, K.; Sternhell, S.; Templeton, J. F.; Tobinaga, S. *Experentia* **1960**, *16*, 41.

(2) For a recent review, see: Taylor, D. A. H. *Prog. Chem. Org. Nat. Prod.* **1984**, *45*, 1.

(3) All reactions involving air-sensitive reactants or products were conducted under dry argon.

(4) Purification by silica gel chromatography using (a) hexane–ethyl acetate and (b) hexane–ether.

(5) See: Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742, 7612.

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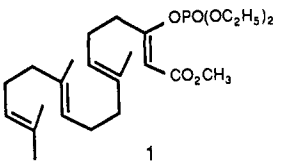
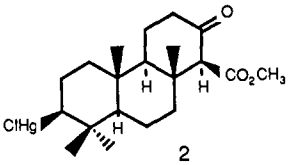
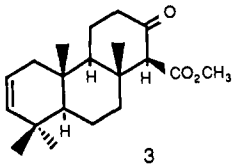
by diethyl chlorophosphate at 0 °C for 30 min, 91% yield) and thence by reaction with 6 equiv of diisobutylaluminum hydride at −78 °C in toluene into allylic alcohol **5** (75%). The alcohol



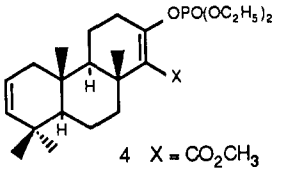
1



2

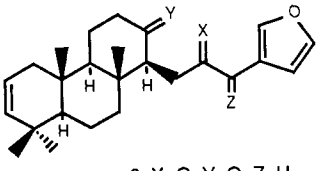


3

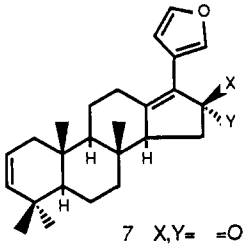


4 X = CO_2CH_3
5 X = CH_2OH

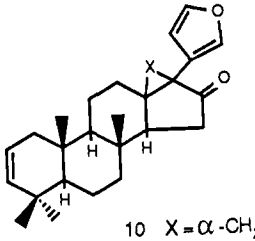
5 was elaborated to diketone **6** (90% yield) in one flask by using a combination of Michael and Nef reactions according to the following process: (1) slow addition (20 min) of an ethanolic solution of **5** to an ethanolic solution of the sodium salt of 3-(2-nitroethyl)furan[6] at reflux (total reaction time 45 min) and (2) cooling to 10 °C and rapid addition to a solution of 12 N HCl–ethanol (1:3.3) at 10 °C. Exposure of **6** to 1 M sodium ethoxide in ethanol at 56 °C for 45 min produced crystalline tetracyclic enone **7**[4a] (80%). Reduction of **7** using L-Selectride in THF at −78 °C afforded stereospecifically the 16β-alcohol **8** (95%), which was inverted to the 16α-alcohol **9** by (1) reaction with benzoic acid, triphenylphosphine, and diethyl azodicarboxylate in THF at 0 °C for 2 h followed by (2) saponification with ethanolic potassium hydroxide (50% overall).



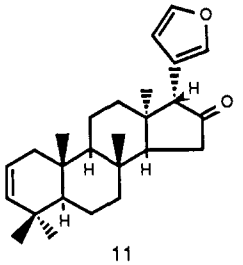
6 X=O, Y=O, Z=H_2
14 X=O_2, Y=CH_2, Z=N_2



7 X,Y= =O
8 X = OH, Y = H
9 X = H, Y = OH

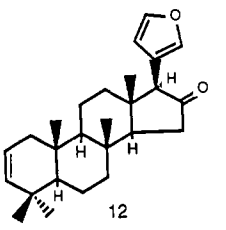


10 X = α-CH_2
13 X = β-CH_2

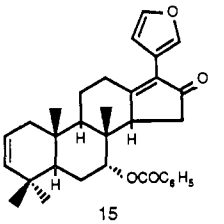


11

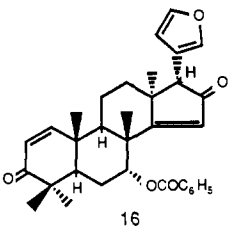
With intermediates **6–9** in hand the stage was set for the difficult task of introducing the C/D angular methyl group. The most obvious approach, conjugate addition of methyl to tetracyclic enone **7**, was unsuccessful with a wide variety of reagents, doubtless because of steric retardation.[7] Stereospecific introduction of methyl at C(13) in either the 13α (limonoid) or the 13β configuration could be realized using the hydroxyl-directed Simmons–Smith process. Reaction of 16α-alcohol **9** and ethereal Simmons–Smith reagent (prepared from methylene iodide and Zn–Ag couple[8]) at 0 °C for 2 h provided a single cyclopropyl carbinol (89%) that upon oxidation (pyridinium dichromate, powdered 3A molecular sieves in methylene chloride at 23 °C for 3 h) gave cyclopropyl ketone **10** (96%). Reduction of **10** with lithium–liquid ammonia at −78 °C for 15 min afforded the desired limonoid **11** (92%). The isomeric tetracyclic ketone **12** was prepared by a parallel sequence from 16β-alcohol **8** via ketone **13**. The stereochemical assignments in each series were confirmed by 500-MHz ^1H NMR data (spin decoupling and NOE measurements) obtained for **11** and **12**. Irradiation of the C(13) methyl substituent of **11** (δ 0.76, $CDCl_3$ solution) produced an NOE effect on 14α-H, 15α-H, and the two furan protons vicinal to the C-(17)–furan linkage. For **12** in C_6D_6 solution positive NOE effects were observed between the methyl group attached to C(13) (δ 0.54) and the following: two furan protons (δ 7.61 and 6.27), H(15β), and the methyl attached to C(8) (δ 0.69). Further, the C(8) methyl group of **12** showed a positive NOE with the C(13) methyl (δ 0.54) and also the C(10) methyl (δ 0.88). In turn, the C(10) methyl of **12** showed a positive NOE to the 4β-methyl (δ 0.98). Irradiation of the remaining 4α-methyl of **12** (δ 1.07) resulted in a positive NOE with the C(3) olefinic proton (δ 5.52).



12



15



16

Another route to the 13-*epi*-limonoid skeleton was demonstrated by using diazo ketone **14** derived from diketone **6**.[9] Slow addition of **14** to a suspension of rhodium(II) acetate in toluene produced selectively cyclopropyl ketone **13**, which was converted cleanly to **12** (Li–NH_3 as described above). It is of considerable interest that this internal cyclopropanation route leads to only trans-fused 6/5 product **12**.

The allylic alcohol **5** can be functionalized at C(7) by Barton's nitrite photolysis method and the resulting 7-oxime converted to 7α-alcohol and 7α-benzoyloxy derivatives. Annulation of the 7α-benzoate as described above furnished the teracyclic keto benzoate **15** by a sequence paralleling that used for the synthesis of **7**. This product is suitably functionalized for conversion to several naturally derived limonoids, for example, azadiradione (**16**).[2,10]

The synthetic approach to limonoids described herein is short and stereocontrolled. Its brevity stems from the effective dovetailing of two powerful annulation methods.

Acknowledgment. This work was assisted financially by a grant from the National Institutes of Health.

Supplementary Material Available: ^1H NMR, IR, and mass spectral data for synthetic intermediates (3 pages). Ordering information is given on any current masthead page.

(6) 3-(2-Nitroethyl)furan was prepared from furan-3-carboxaldehyde by condensation with nitromethane and subsequent reduction with sodium borohydride.

(7) Various organocopper reagents derived from CuI or CuCN with CH_3Li or $(CH_3)_2Zn$ were tried in the absence or presence of electrophilic promoters $BF_3{\cdot}Et_2O$ or $(CH_3)_3SiCl$. Only unreacted enone **7** or 1,2-carbonyl addition product could be recovered.

(8) Conia, J. M.; Denis, J. M.; Girard, C. *Synthesis* **1972**, 549.

(9) The sequence used was (1) enol silylation with *tert*-butyldimethylsilyl triflate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at 0 °C for 11 h, (2) reaction with methylenetriphenylphosphorane in toluene at 0 °C followed by acidic workup, and (3) reaction with tosyl azide–DBU in THF.

(10) Kraus, W.; Cramer, R.; Sawitzka, G. *Photochemistry* **1981**, *20*, 117.