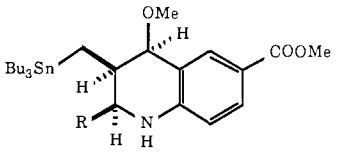
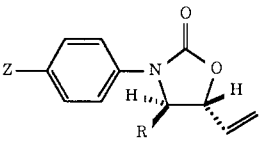
aldehydes and simple aliphatic amines,[14] or even to the behavior of moderately activated benzalaniline[4] (Table III, entry 2i), which reacted slowly and in poor yield with oxygenated stannanes. Similarly, imine **21**, a compound in which activation by the *N*-carbomethoxyphenyl substituent is mesomerically reduced by a methoxy group, also underwent slow reaction only at room temperature, with consequent erosion of diastereoselectivity. Condensations with oxygenated stannanes were, of course, of particular interest to us. [(1*Z*)-1-[(Tetrahydropyranyl)oxy]propen-3-yl]tributyltin appeared to be the reagent of choice, affording products more stereoselectively and in better yield than [(1*Z*)-1-methoxypropen-3-yl]tributyltin. Furthermore, boron trifluoride promoted condensations of the latter reagent with imines **2f** and **2g** were marred by a competing Povarov reaction,[15] which gave dihydroquinolines **6**. Compound **6b** was in fact the major product



6a: R = Ph (17%)
6b: R = iBu (41%)

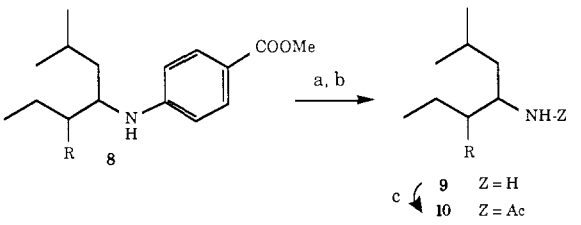


7

of the reaction between the stannane and **2g**. Interestingly, the dihydroquinolines were formed as single stereoisomers of all-cis stereochemistry (300-MHz ^{1}H NMR), suggesting an endo topological course for the Povarov cyclocondensation. This intriguing mode of reactivity was repressed by the use of the OTHP organometallic, presumably as a result of "anomeric" withdrawal of electron density from the vinyl ether oxygen, and consequent decrease in the nucleophilicity of the carbon atom β to oxygen in the enol ether system.

Diastereoselectivities varied from 3:1 to a substantial 10:1 in favor of the predicted syn product,[16] in agreement with the Seebach rule[17] and with other acyclic transition state models for similar additions to π-systems.[2,5] Stereochemical assignments were made by extensive NOE measurements[18] on oxazolones **7**;[19] results of these studies

Scheme I[a]



8/9/10a: R = H; 8/9/10b: R = OTHP

[a] (a) Aqueous NaOH, MeOH, reflux; (b) Li, NH_3(l), THF, tBuOH, add NH_4Cl; (c) Ac_2O, pyridine, 70–80% overall.

allowed subsequent stereochemical assignment in the methoxy series. It is noteworthy that diastereoselectivities, as well as yields, were not affected by the thermal history of the imine–Lewis acid mixture,[3] doubtless because of the rapidity with which condensations occurred.

Release of the nitrogen functionality from its aryl activating group added a useful new dimension to the new 1,2-amino alcohol synthesis. Thus, Birch-type reduction[20] (Li, NH_3/THF, tBuOH) of the acids[21] obtained by base hydrolysis of representative substrates **8** yielded the expected free amines, conveniently characterized as the acetamides (80% overall chromatographed yield) (Scheme I).

In conclusion, we have demonstrated the condensation of activated imines with allylstannanes under catalysis by the nonchelating BF_3OEt_2. The foundations are now established for a future study of issues of Cram–Felkin-type vs chelation-controlled reactivity with α-heterosubstituted imines and consequent development of an asymmetric variant of the new chemistry. We are actively investigating these matters and will report on additional developments in due course.

Acknowledgment. We thank the National Science Foundation (Grant CHE-8708130) and the Robert A. Welch Foundation (Grant C-1007) for their generous support of this work.

Supplementary Material Available: Experimental procedures for the preparation of activated imines and for their condensation with allylstannanes, spectral data for selected new compounds, hardcopy ^{1}H spectra of representative imines (16 pages). Ordering information is given on any current masthead page.

(14) We confirmed that these substances are unreactive towards allylstannanes: see discussion in ref 4.
(15) Cf. (a) Povarov, L. S. *Izv. Akad.Nauk. SSSR, Ser. Khim.* **1966**, 337 (*Chem. Abstr.* **1966**, *64*, 17539). (b) Elslager, E. F.; Worth, D, F. *J. Heterocyl. Chem.* **1969**, *6*, 597. For a review of similar reactions see: Jones, G. In *Comprehensive Heterocyclic Chemistry*; Katritzsky, A. R., Rees, C. W., Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, U.K., 1984; Part 2A, pp 395–510, in particular pp 450–453. Interestingly, Povarov reactions did not interfere with condensation of the methoxystannane with imine **21**.
(16) Diastereoselectivities were determined by comparison of the integrated 300-MHz proton NMR spectra of crude **4/5** and of crude oxazolidinones **7**, thus removing ambiguities resulting from the presence of diastereomers at the level of the stereogenic carbon of undefined stereochemistry at the anomeric position of the THP moiety of **4/5**.
(17) Seebach, D.; Golinsky, J. *Helv. Chim. Acta* **1981**, *64*, 1413.
(18) We thank Dr. Alan M. Kook, of this department, for performing all the NOE measurements.
(19) The oxazolidinones were prepared from compounds **4/5** by treatment with dilute aqueous HCl (MeOH; 90–95%) followed by phosgenation (toluene/pyridine, 90%) and chromatographic purification.
(20) Recent review: Hook, J. M.; Mander, J. N. *Nat. Prod. Rep.* **1986**, *3*, 35.
(21) Direct reduction of the esters (Rabideau, P. W.; Huser, D. L.; Nyikos, S. J. *Tetrahedron Lett.* **1980**, *21*, 1401) was difficult.
(22) Bigelow, L. A.; Eatough, H. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 80.

Regioselective Synthesis of (±)-11-Nor-9-carboxy-Δ^9-THC

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Summary: The regioselective synthesis of (±)-11-nor-9-carboxy-Δ^9-THC (1) has been carried out in eight steps and 14% yield from apoverbenone (**10**) and the bis-MOM ether of olivetol.

Sir: 11-Nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid (11-nor-9-carboxy-THC, 1), a principal human metabolite of Δ^9-tetrahydrocannabinol (THC, 2), is the compound detected in the analytical procedures designed to ascertain

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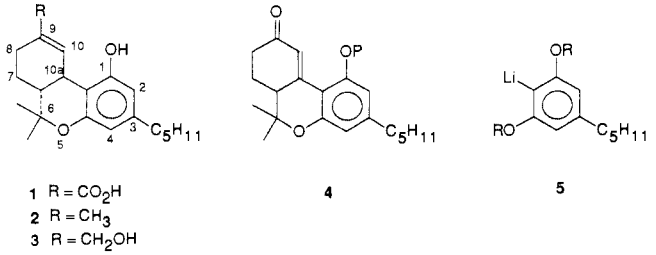
Scheme I



1 R = CO_2H
2 R = CH_3
3 R = CH_2OH

4 5

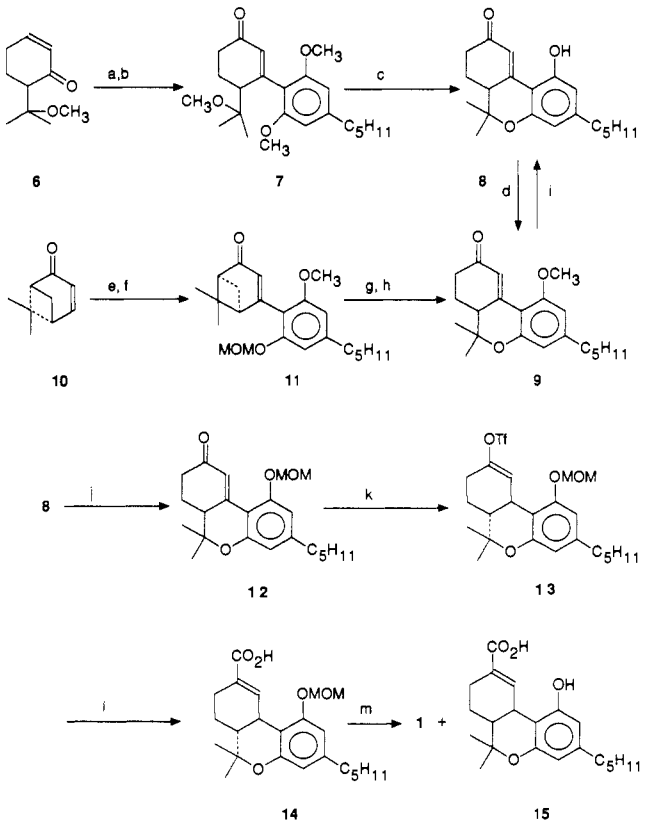
if an individual has used marijuana.[1] Although acid 1 is of considerable forensic importance, the only reported synthesis is that of Pitt et al. in which 11-hydroxy-Δ^9-THC (3) is oxidized in two steps and rather poor yield to acid 1.[2] Several syntheses of alcohol 3 or the corresponding aldehyde have been reported; however, most suffer from a lack of regioselectivity in the initial acid-catalyzed condensation between an alicyclic unit and olivetol.[2,3] A second complicating factor in the synthesis of cannabinoids in general is the instability of the Δ^9 relative to the Δ^8 isomer. Synthesis of 11-oxygenated cannabinoids in which the double bond is introduced by elimination invariably afford a preponderance of the Δ^8 isomer.[3a,4] We now describe a concise, completely regioselective synthesis of racemic acid 1 in 14% overall yield from readily available materials which avoids completely the troublesome oxidation of alcohol 3 or the corresponding aldehyde. This synthesis also makes use of a new synthetic approach to the tricyclic cannabinoid nucleus.

It was envisioned that protected tricyclic enone 4 (Scheme I) would serve as a key intermediate and that the 10,10a-olefin would be used to generate the trans ring fusion and 9,10-olefin. Although enone 4 (P = H) was prepared a number of years ago by the Hoffmann-LaRoche group,[5] this rather classical synthesis did not appear to be particularly versatile nor is it easily adaptable to the synthesis of optically active products. An alternative, convergent synthesis in which an appropriately substituted aryllithium (5) is condensed with an alicyclic ketone seemed more efficient for a general synthetic approach to cannabinoids.

Two conceptually similar but somewhat different approaches to enone 4 were explored, one employing the reaction of cyclohexenone 6[6] (Scheme II) with (2,6-dimethoxy-4-pentylphenyl)lithium to give an unstable tertiary alcohol which on Jones oxidation[7] gave enone 7. Reaction of enone 7 with BBr_3 afforded 8, although in poor overall yield. Enone 8 prepared by this procedure was identical with a sample, mp 199–200 °C, synthesized by the published method.[5] It was, however, difficult to purify, and in practice the crude material was converted directly to methyl ether 9.[6] Enone 6 was prepared by the reaction of the TMS enol ether of cyclohexenone with 2,2-dimethoxypropane under standard Mukaiyama conditions.[8]

The second approach employed the condensation of (+)-apoverbenone (10)[9] with the organolithium derived from the methoxymethylene (MOM) ether of 3-methoxy-5-pentylphenol followed by oxidation to give enone 11.[6] Hydrolysis of the MOM ether and acid-catalyzed cyclization gave racemic 9.[10] This approach to enone 9 proceeds

Scheme II[a]



[a] (a) ArLi, THF, 4 h, reflux; (b) Jones reagent, acetone 0 °C, then 25 °C, 30 min, 28% for two steps; (c) BBr_3, CH_2Cl_2, −78 °C then 25 °C, 6 h; (d) Me_2SO_4, K_2CO_3, acetone, 12 h, reflux, 47% for two steps; (e) ArLi, THF, 0 °C, 30 min, 25 °C, 18 h; (f) PCC, CH_2Cl_2, 25 °C, 4 h, 81% for two steps; (g) CH_2Cl_2, TMSBr, 4A molecular sieves, −30 °C 1 h, 0 °C, 9 h, 91% or PPTS, MEK, 18 h, reflux 91%; (h) HOTs, $CHCl_3$ (dried over 3A sieves), 24 h, reflux, 86%; (i) NaH, nPrSH, DMF, reflux, 3 h, 84%; (j) $ClCH_2OCH_3$, iPr_2NEt, CH_2Cl_2, 25 °C, 18 h, 92%; (k) Li, NH_3, THF, −33 °C, 5 min, then $PhNTf_2$, THF, 0 °C → 25 °C, 18 h, 98%, (l) $Pd(OAc)_2$, Et_3N, Ph_3P, HCO_2H, DMF, CO, 18 h, 25 °C, 74%; (m) PPTS, MEK, reflux, 18 h, 83%.

(1) (a) *The Analysis of Cannabinoids in Biological Fluids*; Hawks, R. L., Ed.; NIDA Research Monograph 42, National Institute on Drug Abuse: Rockville, MD, 1982. This monograph describes a number of analytical procedures for human metabolites of THC and a concise summary of the human metabolism of THC. (b) Williams, P. L.; Moffat, A. C. *J. Pharm. Pharmacol.* **1980**, *32*, 445. (c) Law, B.; Mason, P. A.; Moffat, A. C.; Glendle, R. J.; King, L. J. *Ibid.* **1984**, *36*, 289. (d) The numbering system depicted for 1 is that based on the dibenzopyran ring system. An alternative system based on the monoterpene unit is also used for cannabinoids.

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(3) (a) Pitt, C. G.; Hauser, F.; Hawks, R. G.; Sathe, S.; Wall, M. E. *J. Am. Chem. Soc.* **1972**, *94*, 8578. (b) Razdan, R. K.; Uliss, D. B.; Dalzell, H. C. *Ibid.* **1973**, *95*, 2361. (c) Uliss, D. B.; Hendrick, G. R.; Dalzell, H. C.; Razdan, R. K. *Ibid.* **1978**, *100*, 2929. (d) Lander, N.; Ben-Ziv, Z.; Mechoulam, R.; Martin, B.; Nordqvist, M.; Agurell, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 8. For general reviews of cannabinoid synthesis, see: (e) Razdan, R. K. In *The Total Synthesis of Natural Products*; Ap Simon, J., Ed.; John Wiley: New York, 1981; Vol. 4, pp 186–262. (f) Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75.

(4) (a) Schwartz, A.; Madan, P. *J. Org. Chem.* **1986**, *51*, 5463. (b) Ap Simon, J. W.; Collier, T. L.; Guiver, M. D. *Can. J. Chem.* **1982**, *60*, 2804.

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(10) Although enone 11 is optically active, $[\alpha]^{25}_D$ −65°, enone 9 is racemic. Racemization probably occurs either by way of hydride shifts during the acid-catalyzed cyclization or via enolization of 9.

in much better overall yield than that employing 6 (63% vs 13%), and the product is much more easily purified. This approach should be adaptable to the synthesis of optically active cannabinoids if racemization during the cyclization step can be prevented.

The initial synthetic design envisioned that the methyl ether would serve as a protecting group during elaboration of functionality at C-9. However, while it was possible to prepare the methyl ether of 1, conditions could not be found to regenerate the phenolic hydroxyl without affecting other portions of the molecule.[11] To circumvent this problem the more labile MOM ether of 8 (12) was employed. Although 8 could be prepared by demethylation of 9 (overall sequence: 10 → 11 → 9 → 8), a more efficient approach used the lithio derivative of the bis-MOM ether of olivetol (5, R = MOM) as the aromatic synthon. This procedure afforded pure enone 8 in 56% overall yield.

Dissolving metal reduction of MOM ether 12[6] and trapping of the enolate with *N*-phenyltriflimide[12] gave vinyl triflate 13 with moderate stereoselectivity (trans/cis ~ 3/1).[5] Palladium-mediated carboxylation to 14 followed by hydrolysis of the MOM ether[14] gave a mixture of acid 1 and its cis isomer (15). Careful chromatography failed to separate 1 and 15; however, pure acid 1 (22 mg) could be obtained from 52 mg of the mixture by crystallization. The spectral properties of synthetic acid 1 were identical with those of the natural material, and the overall yield of pure 1 from the bis-MOM ether of olivetol and apoverbenone (10) is 14%.

Acknowledgment. We thank the National Institute on Drug Abuse for support of this work under Grant DA-03590. We also thank Drs. Alan Schwartz of Hoffmann-LaRoche and Herbert H. Seltzman of the Research Triangle Institute for spectra of acid 1 and Melissa D. Lee for technical assistance.

(11) In particular, either the double bond migrates into conjugation with the aromatic ring or compounds containing a cis ring fusion are obtained. The details will be described in the full paper.

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Articles

Tubingensin A: An Antiviral Carbazole Alkaloid from the Sclerotia of *Aspergillus tubingensis*

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Tubingensin A (3), a new carbazole alkaloid biogenetically related to the aflavinines, has been isolated from the hexane extract of the sclerotia of the fungus *Aspergillus tubingensis*. The structure of tubingensin A, which contains an unprecedented 9*H*-octahydronaphtho[3,4-*b*]carbazole ring system, was assigned through NMR decoupling, selective INEPT, and heteronuclear shift correlation experiments. Tubingensin A exhibits activity against the widespread crop pest *Heliothis zea* and displays in vitro antiviral activity against herpes simplex virus type 1.

Many fungi produce specially adapted morphological structures called sclerotia that are critical to the long-term survival and propagation of the species.[1-5] Sclerotia can remain dormant in soil for long periods of time, during which they are exposed to predation by fungivorous insects and arthropods.[2,3] Many vascular plants are known to selectively allocate secondary metabolites to important physiological structures as defenses against herbivore predation.[6] However, only the sclerotia of *Claviceps* spp. (which produce the ergot alkaloids) have been commonly explored for the production of unique, biologically active secondary metabolites.[7]

We have previously reported the isolation of four antiinsectan aflavinine derivatives (e.g., 1) that are selectively allocated to the sclerotia of *Aspergillus flavus*.[3,4] The typical sclerotial concentrations of these compounds are sufficient to deter feeding by fungivorous insects that encounter *A. flavus* sclerotia under natural conditions. A

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