Synthesis of (±)-nor-Δ⁹-*cis*-6a,10a-THC-9-carboxylic acid (THC = Tetrahydrocannabinol)

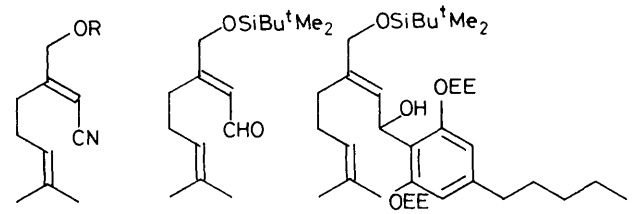
Marcus A. Tius* and Xue-qin Gu

Department of Chemistry, University of Hawaii, 2545 The Mall, Honolulu, Hawaii 96822, U.S.A.

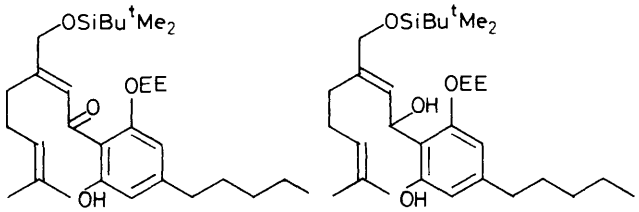
A convenient synthesis of the racemate of the *cis*-6a,10a-isomer of the major human urinary metabolite of Δ⁹-tetrahydrocannabinol has been accomplished.

As a part of our program of synthetic studies directed at the cannabinoids and their metabolites[1] we have examined strategies aimed at improved syntheses of the most important human metabolites and methods that provide access to structurally unique analogues. Much of the early work in this area was to confirm the structures of the metabolites and to provide materials for the evaluation of biological activity.[2] A continuing research interest in these compounds is driven by the commercial need for metabolites of Δ⁹-THC (THC = tetrahydrocannabinol) as analytical standards in the calibration of assays for the accurate detection of cannabinoids in urine,[3] and the development of new pharmaceutical agents modelled after the cannabinoids.[2,4] We disclose an effective synthesis of the *cis*-6a,10a isomer of nor-Δ⁹-THC-9-carboxylic acid (**1**).

It is useful to consider (**1**) as being composed of a terpene-derived fragment and olivetol. The challenge is to couple olivetol with a terpene in which C(11) is oxidized, in order to avoid the inefficiencies of multiple functional group manipulations. A convenient source of the terpene fragment was *E*-3-hydroxymethyl-7-methylocta-2,6-dienenitrile (**2**). This material was prepared from α-phenylsulphinylacetonitrile and 6-methylhept-5-en-2-one according to a literature procedure.[5] The hydroxy group which was destined to be oxidized to the C(11) carboxylic acid was first protected as the t-butyldimethylsilyl ether (**3**) in >95% yield.[6] The reduction of the nitrile to aldehyde (**4**) took place in 96% yield by treatment in ether at −5 °C with di-isobutylaluminium hydride. In a subsequent step, the bis-2-ethoxyethyl ether of olivetol was metallated[7] [n-butyl-lithium in tetrahydrofuran (THF) at −15 to 25 °C] and (**4**) was added. The secondary alcohol (**5**) was produced in 68% yield. All carbon atoms of the final product (**1**) were present in (**5**). Furthermore, solvolysis of the secondary, allylic, benzylic alcohol was expected to initiate the crucial cyclization reaction. Participation of the phenolic oxygen atom of the ethoxyethyl group was expected to lead directly to (**8**), following loss of an oxygen-stabilized cationic fragment. The treatment, however, of (**5**) under a variety of reaction conditions, either with protic or Lewis acids, invariably produced complicated reaction mixtures which contained minor amounts of cyclized product. Since the complete failure of the cyclization reaction appeared

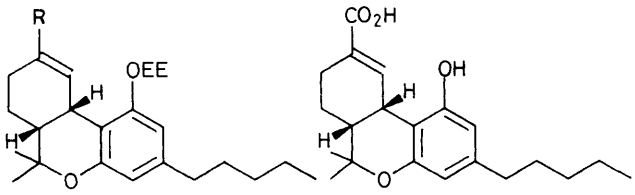


(2) R = H (4) (5)
(3) R = SiBu^{t}Me$_2$

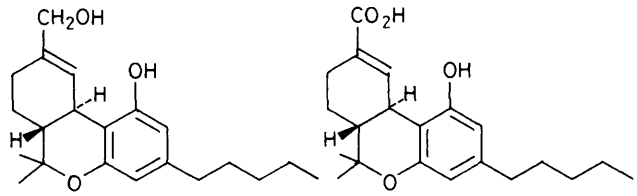


(6) (7)

OEE = EtOCHCH$_3$



(8) R = CH$_2$OSiBu^{t}Me$_2$ (1)
(9) R = CH$_2$OH
(10) R = CHO
(11) R = CO$_2$H



(12) (13)

OEE = EtOCHCH$_3$

to have been caused by competitive protonation of the ethoxyethyl protecting groups,[8] their removal prior to cyclization was indicated. This posed a problem, because all acid-catalysed hydrolyses of the ethoxyethyl groups led to the same mixtures of products as the cyclization reaction.

This problem was overcome in a unique way. The oxidation of (**5**) with azodicarbonyl-dipiperidine in the presence of t-butoxymagnesium bromide[9] led cleanly and in 79% yield to compound (**6**). Oxidation of the alcohol was accompanied by loss of only one of the two ethoxyethyl protecting groups. The selectivity and the conditions for the loss of the protecting group were surprising, but may have resulted from a process involving initially a rapid proton exchange between (**5**) and the bromomagnesium alkoxide. Subsequent chelation of the magnesium by one of the two phenolic oxygen atoms through a six-membered ring could assist the fragmentation and the loss of the acetal protecting group. The oxidation of the benzylic alkoxide by the azodi-imide would produce (**6**). Presumably, loss of the second group from (**6**) does not take place because of the formation of a magnesium chelate between the carbonyl and the phenoxide. The loss of only one of the protecting groups from (**5**) was fortunate because (**7**), the product of reduction of (**6**) by sodium borohydride (94% yield), was an ideal substrate for the cationic cyclization. Treatment of (**7**) with trifluoroacetic acid in dry chloroform at 0 °C led rapidly to (**8**) (69% isolated yield) and a small amount of an isomer. The presence of diastereoisomers due to the asymmetric centre of the ethoxyethyl protecting group made the interpretation of the n.m.r. spectrum of the product mixture quite difficult; however, it appeared that the *cis*/*trans* ring junction isomers had formed in the approximate ratio of 6:1. In order to confirm this, the cyclization reaction was repeated with the triol in which the ethoxyethyl group had been removed. This triol was prepared from (**6**) in two steps: firstly, ethoxyethyl group removal was accomplished in 60% yield by treatment for 12 h at 25 °C with a 1:1:1 mixture of acetic acid, THF and water; secondly, reduction of the phenone with sodium borohydride in methanolic tetrahydrofuran at 0 °C was accomplished in 64% yield. The triol was cyclized in 58% yield under the same conditions as (**7**). The ^{1}H n.m.r. spectrum for the product of this related cyclization indicated that a 6:1 ratio of *cis* and *trans* ring fused products has been formed. It is noteworthy that both the acid labile oxygen protecting groups of (**7**) were retained in the product. The ^{1}H n.m.r. spectrum of (**8**) showed conclusively that the ring junction stereochemistry of the major cyclization product was *cis*. The C(10a) proton in (**8**) appeared at δ 3.61 as a broad singlet ($w_{\frac{1}{2}}$ 12 Hz) as expected for the *cis* stereoisomer.[10] The chemical shift and the appearance of this proton were similar in compounds (**9**), (**10**), (**11**), and (**1**). In (−)-11-nor-Δ^9-tetrahydrocannabinol-9-methanol (**12**) and (−)-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid (**13**), which have a *trans* ring fusion, the C-10a proton appears as a doublet of doublets (J 10.5, 1.5 Hz) at δ 3.37.[1,11] The conversion of (**8**) to (**1**) was accomplished in a straightforward manner. Silyl ether cleavage with tetra-n-butylammonium fluoride in THF at −25 °C produced allylic alcohol (**9**) in 65% yield. Oxidation to aldehyde (**10**) with Mukaiyama's reagent took place in 79% yield. Further oxidation to carboxylic acid (**11**) was accomplished by exposure to sodium chlorite in the presence of 2-methylbut-2=ene in 79% yield.[12] Hydrolytic removal of the phenolic ethoxyethyl acetal with pyridinium tosylate in methanol led to (**1**) in 76% yield.

The exclusive formation of the *cis* ring fusion during the cyclization reaction can be understood to result from the kinetically controlled intramolecular cycloaddition of an *o*-quinone methide.[7,13] Acid-catalysed opening of the pyranoid ring, followed by reclosing to the thermodynamically favoured *trans* ring fusion, does not take place under the mild conditions for the cyclization reaction.[10a] A fundamental difference between the transition state geometries for the cyclization of cannabinoids with C(8)–C(9) unsaturation and those lacking unsaturation at that position is suggested by the evidence in the literature. Kinetically controlled cyclizations of saturated cannabinoids, under conditions which preclude ring junction isomerization through reversible opening of the pyranoid ring, give rise exclusively to *trans* ring fused products.[7,10a,13] With C(8)–C(9) unsaturated cannabinoids, the same reaction conditions produce *cis* ring fused products.[14]

In conclusion, a synthesis of (±)-nor-Δ^9-*cis*-6a,10a-THC-9-carboxylic acid (**1**) is described.† The unprecedented removal of a phenolic ethoxyethyl group in base was noted, apparently taking place through an anchimerically assisted process.

We acknowledge the National Foundation (CHE86-02328) and the Petroleum Research Fund (17589-AC1). M. A. T. is a fellow of the Alfred P. Sloan Foundation.

Received, 20th February 1989; Com. 9/00766K

References

1 M. A. Tius, X-q. Gu, and M. A. Kerr, *J. Chem. Soc., Chem. Commun.*, 1989, 62.
2 R. A. Archer, P. Stark, and L. Lemberger in 'Cannabinoids as Therapeutic Agents,' ed. R. Mechoulam, pp. 85—103, CRC Press, Boca Raton, Florida, 1986.
3 J. D. Whiting and W. W. Manders, *J. Anal. Toxicol.*, 1982, **6**, 49.
4 L. S. Melvin, M. R. Johnson, C. A. Harbert, G. M. Milne, and A. Weissman, *J. Med. Chem.*, 1984, **27**, 67; M. R. Johnson, L. S. Melvin, T. H. Althuis, J. S. Bindra, C. A. Harbert, G. M. Milne, and A. Weissman, *J. Clin. Pharmacol.*, 1981, **21**, 271S; M. R. Johnson and L. S. Melvin in ref. 2, p. 121.
5 T. Ono, T. Tamaoka, Y. Yuasa, T. Matsuda, J. Nokami, and S. Wakabayashi, *J. Am. Chem. Soc.*, 1984, **106**, 7890.
6 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.
7 J. P. Marino and S. L. Dax, *J. Org. Chem.*, 1984, **49**, 3671.
8 For a recent example see: L. E. Overman and A. S. Thompson, *J. Am. Chem. Soc.*, 1988, **110**, 2248.
9 K. Narasaka, A. Morikawa, K. Saigo, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 2773.
10 (a) M. Moore, R. W. Rickards, and H. Ronneberg, *Aust. J. Chem.*, 1984, **37**, 2339; (b) G. Saucy, R. Marbet, H. Lindlar, and O. Isler, *Helv. Chim. Acta*, 1959, **42**, 1945.
11 K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Am. Chem. Soc.*, 1967, **89**, 5934; D. B. Uliss, G. R. Handrick, H. C. Dalzell, and R. K. Razdan, *ibid.*, 1978, **100**, 2929; C. G. Pitt, M. S. Fowler, S. Sathe, S. C. Srivastava, and D. L. Williams, *ibid.*, 1975, **97**, 3798.
12 R. Pellegata, P. Ventura, and M. Villa, *Synth. Commun.*, 1985, **15**, 165.
13 J. J. Talley, *J. Org. Chem.*, 1985, **50**, 1695.
14 J. M. Luteijn and H. J. W. Spronck, *J. Chem. Soc., Perkin Trans. 1*, 1979, 201; the mechanism for the cyclization which was proposed in this paper is stereochemically untenable in our opinion.

† To the best of our knowledge, this compound has not been described in the literature.