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SYNTHETIC STUDIES ON SICCANIN. EFFICIENT CONSTRUCTION OF THE CIS-FUSED DRIMANE UNIT AND SYNTHESIS OF ISOSICCANIN METHYL ETHER

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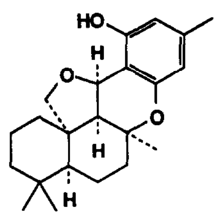
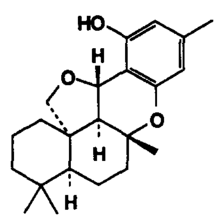
Abstract: Under ferric chloride catalysis, the Diels-Alder addition of dienone ester **3** to diene **4** occurred readily to give adduct **5** which possesses the complete carbon framework of the sesquiterpene unit of siccanin (**1**) with the correct relative stereochemistry. Further elaboration on **5** gave rise to the methyl ether of isosiccanin (**2**), an unnatural diastereomer of the antifungal antibiotic 1.

Siccanin was first isolated by Ishibashi from the culture broth of *Helminthosporium siccans* Drechsler.[1] As shown in formula **1**, this compound possesses a unique structure consisting of an unusual *cis*-fused drimane sesquiterpene unit and an orsellinate moiety.[2] Biologically, it is a highly potent, yet rather nontoxic antifungal antibiotic[3] which is particularly effective against various human pathogenic fungi. Owing to these interesting properties, siccanin (1) and its analogues have been the subject of considerable synthetic activity[3-5] with an elegant total synthesis of the natural metabolite having been recently accomplished.[5] Herein we wish to describe a facile approach to the *cis*-fused drimane system with excellent regio- and stereochemical control as well as the synthesis of the methyl ether of an unnatural diastereomer of **1** which we name isosiccanin (**2**).



1



2

The construction of the sesquiterpene portion of siccanin (1) was facilitated by the observed dienophilicity of enone ester **3**. This compound was shown to undergo Diels-Alder reaction with a variety of 1,3-butadienes resulting in the direct formation of highly functionalized decalin systems with expectable regio- and stereochemistry.[6] Based on these findings, the addition of **3** to diene **4** is expected to give keto ester **5** possessing the complete carbon framework of the desired sesquiterpene unit. Indeed, when enone ester **3** was subjected to Diels-Alder reaction with diene **4**[7] (1.5 eq) in ether under the catalysis of ferric chloride (1 eq), the desired adduct **5** was isolated in 84% yield after 48 h at -20°C (Scheme 1). The structure of this compound could be readily deduced on the basis of the spectral data and the observed mode of cycloaddition of **3** with various dienes.[6] This assignment was unambiguously confirmed at a later stage by X-ray analysis of a derivative.

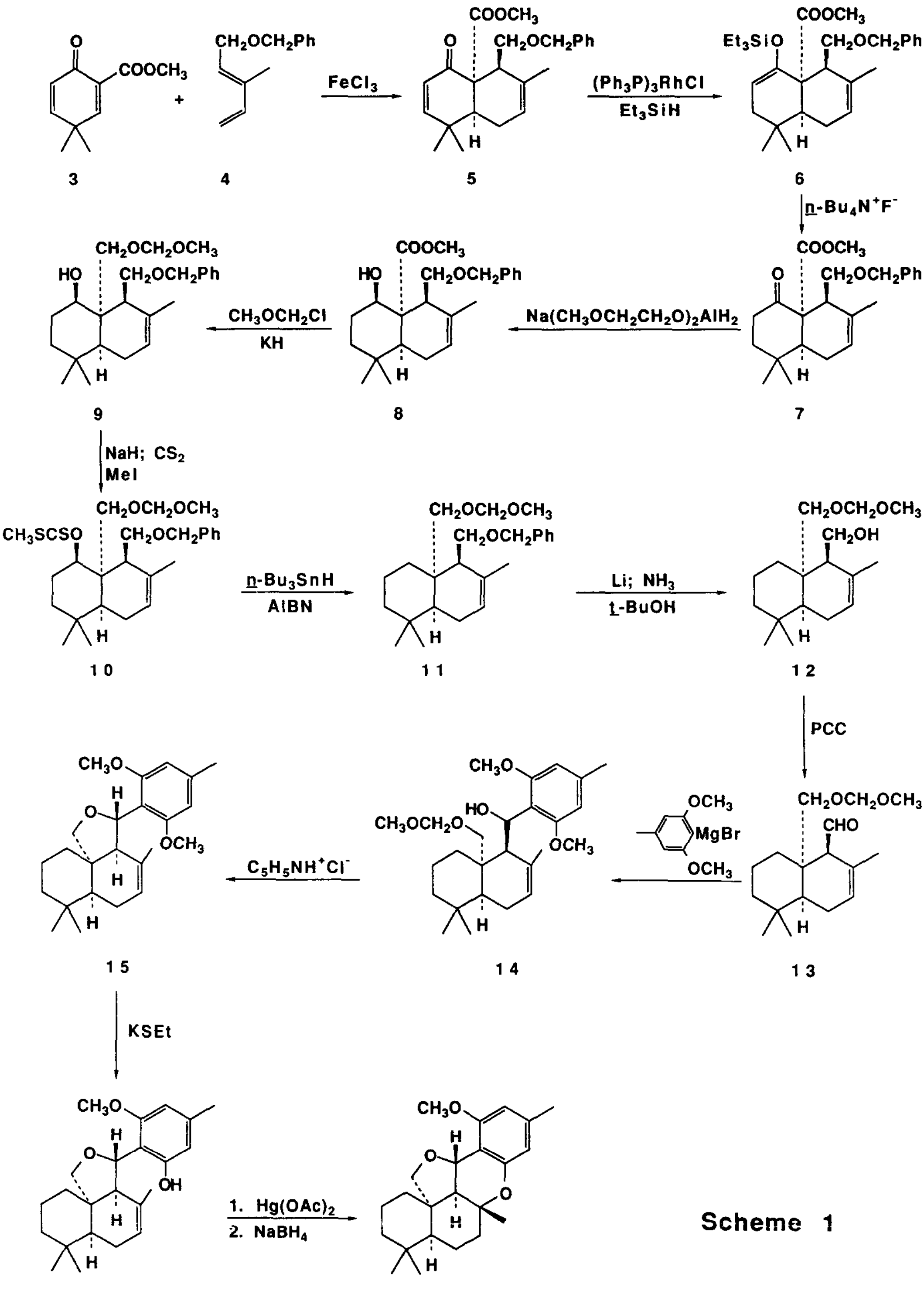
In order to selectively saturate the conjugated carbon-carbon double bond, compound **5** was treated with triethylsilane and a catalytic amount of tris(triphenylphosphine)rhodium(I) chloride in benzene[9] followed by exposure of the resulting silyl enol ether **6** to a solution of tetra-n-butylammonium fluoride in tetrahydrofuran. Keto ester **7** thus obtained in quantitative yield was reduced with sodium bis(2-methoxyethoxy)aluminum hydride at room temperature in ether and toluene giving diol **8** (m.p. 90-92°C; 72% yield), the structure of which was unambiguously determined by a single crystal X-ray analysis.

To remove the successive secondary hydroxyl group, diol **8** was converted to hydroxy ether **9** (72% yield) by treatment with an excess of potassium hydride and a stoichiometric amount of chloromethyl methyl ether at -10°C using 1,2-dimethoxyethane as a solvent. Deoxygenation of **9** was effected via the corresponding xanthate **10** which was readily formed when the former was treated with carbon disulfide, methyl iodide and sodium hydride at room temperature in 1,2-dimethoxyethane. Heating xanthate **10** with tri-n-butyltin hydride[10] and a small amount of azobisisobutyronitrile in degassed toluene at reflux gave the desired ether **11** (93% yield from **9**).

Debenzylation of **11** using lithium in liquid ammonia containing a small quantity of t-butyl alcohol gave rise to alcohol **12**, which was oxidized to the corresponding aldehyde **13** (66% yield from **11**) on exposure to pyridinium chlorochromate[11] in dichloromethane. At this point, the construction of the complete sesquiterpene unit present in the target molecule with the correct stereochemistry and oxidation level has been successfully accomplished in nine steps with 27% overall yield from dienone ester **3**.

The orsellinate moiety was incorporated by the reaction of aldehyde **13** with 2,6-dimethoxy-4-methylmagnesium bromide carried out in ether at a temperature range of -78°C to 20°C. A single stereoisomer **14**, with the undetermined stereochemistry at the newly generated chiral center, was produced in 70% yield.

The transformation of **14** to siccanin **1** requires consecutive closures of two ether rings. On exposure to pyridinium chloride in refluxing dichloromethane, the tetrahydrofuran ring was readily formed and a single product, m.p. 179-181°C, was isolated in quantitative yield. Unfortunately, a single



COOCH3
CH2OCH2Ph
FeCl3
(Ph3P)3RhCl
Et3SiH
Et3SiO
n-Bu4N+F-
CH2OCH2OCH3
CH3OCH2Cl
KH
Na(CH3OCH2CH2O)2AlH2
NaH; CS2
MeI
CH3SCSO
n-Bu3SnH
AIBN
Li; NH3
t-BuOH
CH2OH
PCC
CHO
MgBr
OCH3
CH3O
C5H5NH+Cl-
KSEt
1. Hg(OAc)2
2. NaBH4
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

Scheme 1

crystal X-ray analysis revealed that this compound was the epimer **15**. This compound, which is expected to be thermodynamically more stable than the desired epimer, possesses an incorrect center for **1**. Its demethylation using potassium ethanethiolate[12] in hot dimethylformamide followed by sequential treatment of the resulting phenol **16** with mercuric acetate and sodium borohydride in methanol at room temperature gave isosiccanin methyl ether **17** (48% yield), m.p. 208-209°C, which displayed spectral data [ir ($CHCl_3$ cast) 1616 (Ar-O-R) and 1114 cm^{-1} (R-O-R); nmr ($CDCl_3$) δ 6.32, 6.24 (both s, 1H each, aromatic), 5.56 (br.s, 1H, ArCHO-), 4.16 (d, 1H, J = 8 Hz, -OC**H**H-), 3.80 (s, 3H, $-OCH_3$), 3.56 (dd, 1H, J = 8, J' = 1 Hz, -OCH**H**-), 2.28 (s, 3H, $ArCH_3$), 1.50 (s, 3H, CH_3CO-), 0.84 and 0.82 (both s, 3H each, $-C(CH_3)_2$)] similar but not identical to those reported[2c] for the methyl ether derived from the naturally occurring compound **1**.

Redirection of the latter part of the approach towards the synthesis of siccanin (**1**) is under current investigation.[13]

References and Notes

1. K. Ishibashi, J. Antibiot. Ser. A, **15**, 161 (1962).
2. (a) K. Hirai, S. Nozoe, K. Tsuda, Y. Iitaka, K. Ishibashi, and M. Shirasaka, Tetrahedron Lett., 2177 (1967). (b) K. Hirai, S. Okuda, S. Nozoe, and Y. Iitaka, Acta Cryst., B**25**, 2630 (1969). (c) K. Hirai, K.T. Suzuki, and S. Nozoe, Tetrahedron, **27**, 6057 (1971).
3. For review see: K. Ishibashi, K. Hirai, M. Arai, S. Sugawara, A. Endo, A. Yasumura, H. Masuda, and T. Muramatsu, Ann. Sankyo Res. Lab., **22**, 1 (1970).
4. S. Nozoe and K. Hirai, Tetrahedron, **27**, 6073 (1971); S. Oida, Y. Ohashi, A. Yoshida, and E. Ohki, Chem. Pharm. Bull., **20**, 2634 (1972); A. Yoshida, S. Oida, Y. Ohashi, C. Tamura, and E. Ohki, ibid., **20**, 2642 (1972); S. Oida, Y. Ohashi, and E. Ohki, ibid., **21**, 528 (1973).
5. M. Kato, K. Heima, Y. Matsumura, and A. Yoshikoshi, J. Am. Chem. Soc., **103**, 2434 (1981).
6. H.J. Liu and E.N.C. Browne, Can. J. Chem., **65**, 1262 (1987).
7. Diene **4** was prepared in 83% yield by benzylation of the corresponding alcohol[8] with benzyl bromide and sodium hydride in tetrahydrofuran at room temperature for 8 h.
8. H.J. Liu and P.R. Pednekar, Synth. Commun., **12**, 39 (1982).
9. H.J. Liu and E.N.C. Browne, Can. J. Chem., **59**, 601 (1981).
10. D.H.R. Barton and S.W. McCombie, J. Chem. Soc. Chem. Commun., 1574 (1975).
11. E.J. Corey and J.W. Suggs, Tetrahedron Lett., 2647 (1975).
12. G.I. Feutrill and R.N. Mirrington, Tetrahedron Lett., 1327 (1970).

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