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STEREOCONTROLLED TOTAL SYNTHESIS OF (±)-LUBIMINOL, A SPIROVETIVANE PHYTOALEXIN

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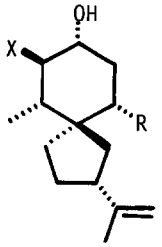
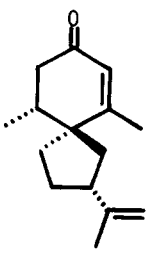
Abstract: A total synthesis of (±)-lubiminol, one of the spirovetivane phytoalexins, was accomplished under a high stereocontrol of all five asymmetric carbon centers.

Since Masamune *et al.*[1] reported the isolation of lubimin (1a) and oxylubimin (1b) from infected potatoes (*Solanum* genus) in 1974, more than ten compounds of highly oxygenated spirovetivane phytoalexins have been assigned and are characterized structurally by the presence of five or six asymmetric carbon centers.[2] These compounds are also of many interest from the viewpoint of their biosynthesis and their biological activities. Although the less oxygenated phytoalexin, solavetivone (2), has been synthesized by several groups,[3] little is known concerning successful synthesis of lubimin-type phytoalxins.[4] In this communication we wish to describe the first synthesis of (±)-lubiminol (dihydrolubimin) (3), isolated from *Solanum* genus infected with *Glomerella cingulata*[5a] or with *Phytophthora infestans*,[5b] under a strict stereocontrol of all five asymmetric centers using a powerful synthon, (2*R**, 5*R**,10*S**)-2-hydroxy-6,10-dimethylspiro[4.5]dec-6-en-8-one[6] (4) which was prepared from the spirodienone (5) *via* the regio- and stereoselective Birch reduction.



1a: R=CHO,X=H
1b: R=CHO,X=OH
3 : R=CH_2OH,X=H



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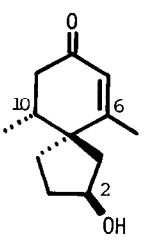

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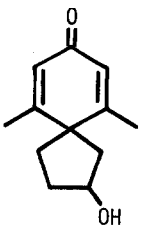

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After the hydroxyl group in 4 was pretected as the pivaloyl ester (6; 92% yield), the enone part was reduced with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in ether at -78°C to afford the single allylic alcohol (7)

[85% yield; δ 1.02(3H,d,*J*=6), 1.15(9H,s), 1.73(3H,s), 4.98(1H,m), 5.22(1H,br s); *m/z* 280(M^+)]. The high stereoselectivity in this reaction should be interpreted in terms of the Baldwin's rule.[7] The methoxymethyl(MOM) ether (8), obtained in 89% yield by reaction of 7 with MOM chloride in the presence of *N,N*-diethylaniline, was oxidized with selenium dioxide in boiling xylene and subsequently reduced with sodium borohydride to provide the alcohol (9)[76% yield; δ 4.02(2H,br s)], which was transformed into the bis-MOM ether (10; 87% yield) in a usual manner. Removal of the pivaloyl group in 10 by the reaction with methyllithium was followed by a usual mesylation of the alcohol (11) to provide the mesylate (12), which was subjected to reaction with the anion of diethyl malonate. The bimolecular substitution reaction smoothly took place and the desired product (13)[ν 1750, 1735; δ 1.24(6H,t,*J*=7), 3.17(1H,d,*J*=10); *m/z* 442(M^+)] was obtained in 57% yield from 11.[8] Hydrogenation of 13 over Raney nickel afforded the spirodecane (14)[97% yield; ν 1752, 1735; δ 1.26(6H, t,*J*=7), 3.13(1H,d,*J*=10,C_2-C<u>H</u>), 4.15(4H,q,*J*=7); *m/z*(CI) 445(M^++1)] as a sole stereoisomer.[9]

Transformation of the bis(ethoxycarbonyl)methyl group at the C-2 position in 14 to the 1-(hydroxymethyl)vinyl one was efficiently achieved by a modification of the known method.[10] Namely, the sodium salt of 14 was reduced with a large excess of Red-Al[11] in boiling dimethoxyethane to afford the expected product (15)[ν 3610, 3400, 1650; δ 4.07(2H,br s,C_2-C-C<u>H</u>$_2$OH), 4.87(1H,d,*J*=1, vinyl H), 4.99(1H,d,*J*=1,vinyl H); *m/z* 312(M^+-HCHO)] in *ca.* 50% yield.[12] The saturated alcohol (16), which was easily prepared by catalytic hydrogenation of 15 over Raney nickel in 91% yield, was mesylated and then hydrolyzed with 3*N* hydrochloric acid in THF at room temperature to give the diol mesylate (17) in 63% yield. Finally, on treatment with sodium iodide and DBU in boiling dimethoxyethane, 17 gave (±)-lubiminol (3)[76% yield; mp 114-116°C; ν 3590, 3400, 1640; δ 0.93(3H,d,*J*=6.5), 1.73(3H,s), 4.68(2H,s); *m/z* 238(M^+), 107 (base)]. The synthetic product was found to be identical with natural lubiminol (3) by means of direct comparison of IR and ^{1}H-NMR spectra. Since lubiminol (3) was already transformed into isolubimin (18),[13] the present work also means a formal synthesis of (±)-isolubimin.

ACKNOWLEDGEMENT We are extremely grateful to Professors A. Stoessl and A. Murai for making available to us samples of natural dihydrolubimin and lubiminol diacetate, and copies of their IR, ^{1}H-NMR and mass spectra.

REFERENCES AND FOOTNOTES

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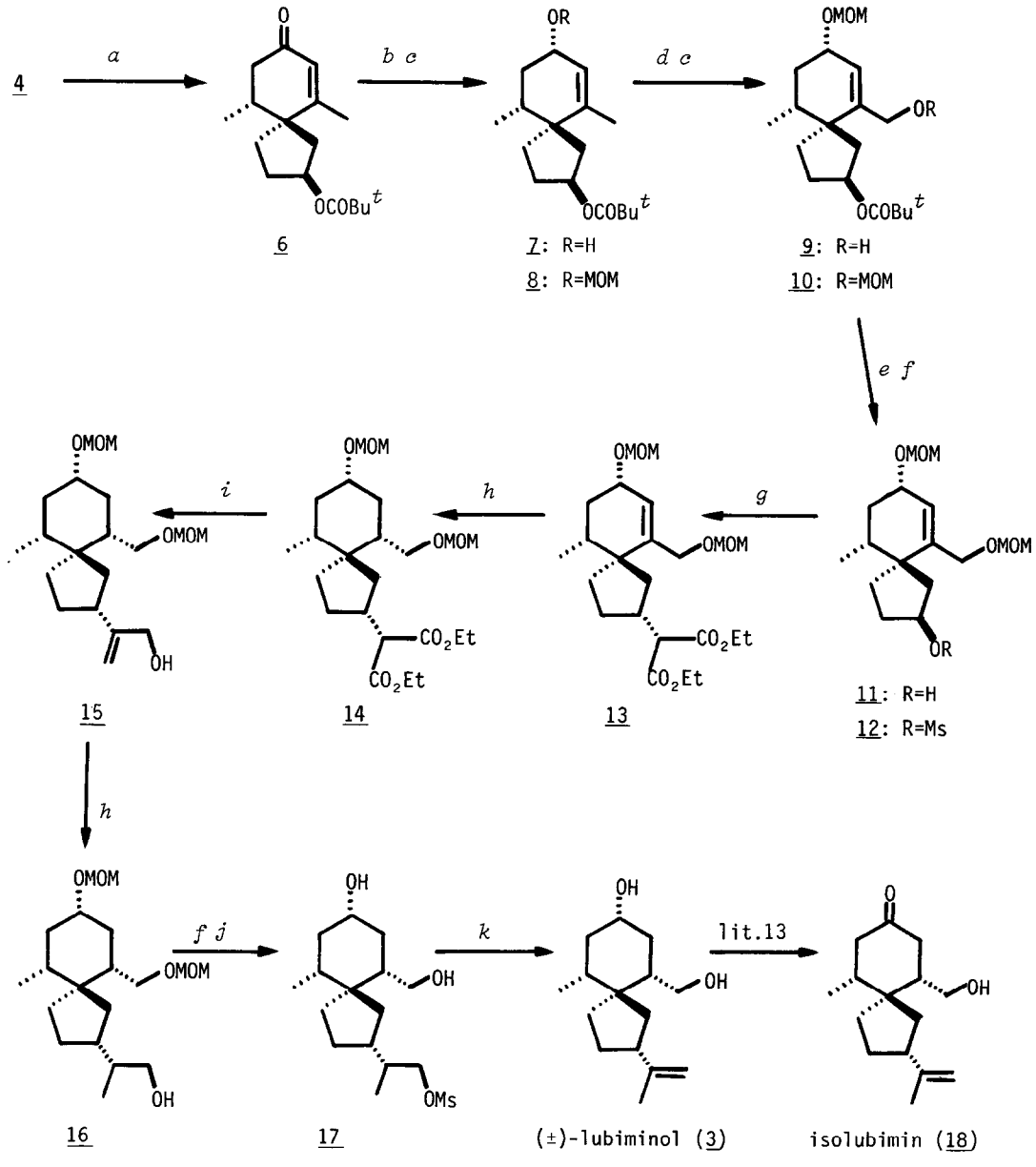
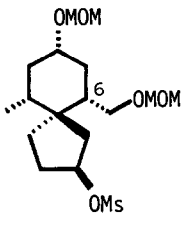
3. *a*) K. Yamada, S. Goto, H. Nagase, and A.T. Christensen, *J.C.S., Chem. Commun.*, 554 (1977); *b*) C. Iwata, T. Fusaka, T. Fujiwara, K. Tomita, and M. Yamada, *ibid.*, 463 (1981); *c*) A. Murai, S. Sato, and T. Masamune, *Tetra-*



Reagents: *a* t-BuCOCl,pyridine,50°C; *b* Red-Al,ether,-78°C; *c* MOM-Cl,$PhNEt_2$, r.t.; *d* SeO_2,xylene,reflux; then $NaBH_4$,MeOH,0°C; *e* MeLi,ether,0°C; *f* MsCl, pyridine,0°C; *g* $NaCH(CO_2Et)_2$,DME,reflux; *h* H_2,Ra-Ni(W2),EtOH,r.t.; *i* NaH, DME,reflux; then Red-Al,DME,reflux; *j* 3*N* HCl,THF,r.t.; *k* NaI,DBU,DME,reflux.

hedron Lett., 22, 1033 (1981); *J.C.S., Chem. Commun.*, 904 (1981).

4. A total synthesis of (±)-lubimin (1) was recently reported: A. Murai, S. Sato, and T. Masamune, *J.C.S., Chem. Commun.*, 513 (1982).
5. *a*) A. Stoessl and E.W.B. Ward, *Tetrahedron Lett.*, 3271 (1976); *b*) N. Katsui, A. Matsunaga, H. Kitahara, F. Yagihashi, A. Murai, T. Masamune, and N. Sato, *Bull. Chem. Soc. Japan*, 50, 1217 (1977).
6. C. Iwata, M. Yamada, Y. Shinoo, K. Kobayashi, and H. Okada, *J.C.S., Chem. Commun.*, 888 (1977); C. Iwata, K. Miyashita, Y. Ida, and M. Yamada, *ibid.*, 461 (1981). This compound was proved to be a useful synthon for (±)-solavetivone,[3b] (±)-agarospirol, and (±)-hinesol [C. Iwata, Y. Ida, K. Miyashita, T. Nakanishi, and M. Yamada, *Chem. Ind.*(London), 165 (1982); *Chem. Pharm. Bull.*, 30, 2738 (1982)].
7. J.E. Baldwin, *J.C.S., Chem. Commun.*, 738 (1976).
8. On the other hand, the saturated mesylate (19), which was obtained by an initial hydrogenation of 9 and subsequent usual transformation, was reacted with the sodium salt of diethyl malonate to afford a small amount of the desired product (14; 14% yield) along with undefined compounds. The lower reactivity of 19 than 12 should be attributable to the steric hindrance of the protected hydroxymethyl group at the C-6 position.
9. Catalytic hydrogenation of 9 over Raney nickel afforded a 5:1 mixture of two diastereoisomers (20a and 20b), stereochemistry of which was confirmed by their ^{13}C-NMR spectral consideration (γ-effect) as compared with those for lubiminol (3) and epilubiminol (21). See, A. Stoessl, J.B. Stothers, and E.W.B. Ward, *Can. J. Chem.*, 56, 645 (1978).
10. J.A. Marshall, N.H. Andersen, and A.R. Hochstetler, *J. Org. Chem.*, 32, 113 (1967).
11. We have found that Red-Al is more efficient for the present purpose than $LiAlH_4$ [Unpublished work].
12. The allylic alcohol (15) was readily converted into (±)-lubiminol bis-MOM ether (22) *via* the mesylate (23), but all attempts to remove the MOM groups were fruitless.
13. N. Katsui, F. Yagihashi, A. Murai, and T. Masamune, *Bull. Chem. Soc. Japan*, 55, 2424 (1982).



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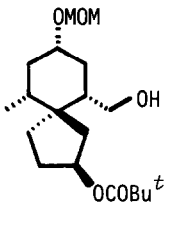
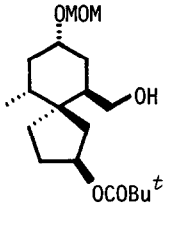


20a



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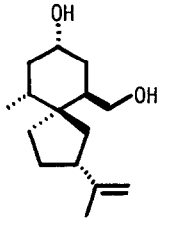

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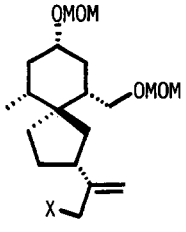

22: X=H
23: X=OMs

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