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ENANTIOSELECTIVE SYNTHESIS OF BISLACTONE STRUCTURE: A FORMAL SYNTHESIS OF (-)-CANADENSOLIDE

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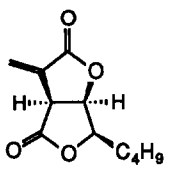
Summary: An enantioselective synthesis of the canadensolide-type bislactone (**12**) via the versatile pyranone (**4**) derived from the chiral furylcarbinol (R)-**3** has been accomplished. A formal synthesis of (-)-canadensolide (**1**) is also described.

The bislactone skeleton has been observed as a common structural feature in antifungal mold metabolites such as avenaciolide,[1] isoavenaciolide,[2] and canadensolide (**1**).[3] A number of method for the construction of the bislactone skeleton have been developed to synthesize these metabolites.[4-6] As part of our continuing studies toward asymmetric syntheses of oxygenated natural products employing the pyranones as versatile intermediates derived from chiral furylcarbinols,[7] we report here an enantioselective synthesis of the canadensolide-type bislactone.



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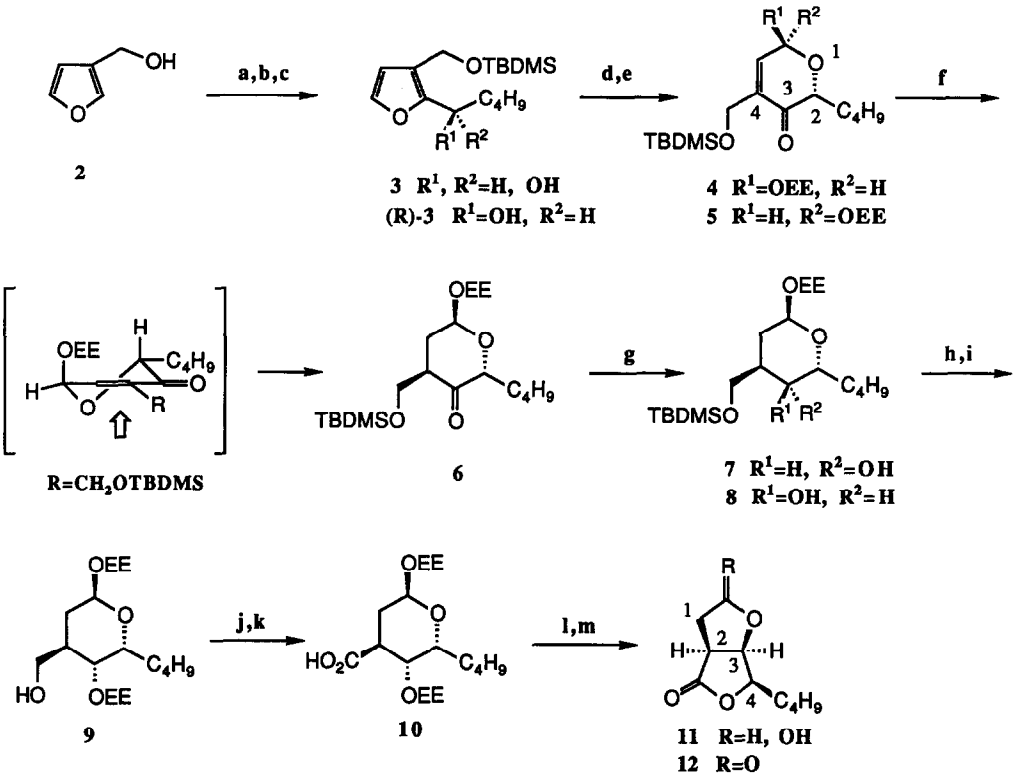
Our synthesis is based on the stereocontrolled construction of three contiguous chiral centers at C-2, C-3, and C-4 on a pyran ring utilizing sequential stereoselective reduction of a 6-alkoxy-2H-pyran-3(6H)-one.

The requisite chiral pyranone (**4**) was prepared as shown in Scheme 1. Addition reaction of the dilithio salt[8] of 3-furanmethanol (**2**) to n-valeraldehyde afforded the 2-furylcarbinol, whose primary alcohol was selectively protected as its silyl ether to give **3**.[9] Kinetic resolution[7c,10] of **3** employing the Sharpless reagents[11] furnished the resolved furylcarbinol (R)-**3** in 41 % yield. The enantiomeric excess of (R)-**3** was determined to be > 95 % ee by the ^{1}H-NMR analysis of the corresponding Mosher's ester.[12] Ring enlargement of (R)-**3** with m-chloroperbenzoic acid afforded the diastereomeric lactols, which were protected as the corresponding ethoxy



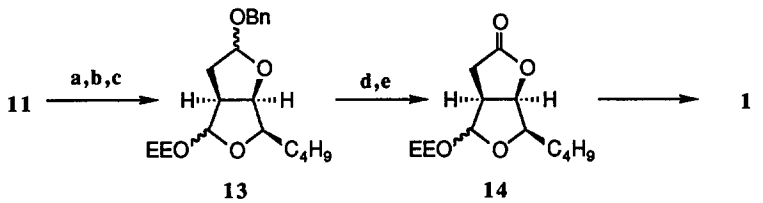
Scheme 1. *Reagents:* a) BuLi (2.2 eq.), THF then C_4H_9CHO (70 %); b) t-$BuMe_2SiCl$, imidazole, DMF (77 %); c) L-DIPT (0.24 eq.), $Ti(Oi\text{-}Pr)_4$(0.2 eq.), t-BuOOH (0.6 eq.), CH_2Cl_2 -25°C (41 %); d) m-CPBA, AcONa, $CHCl_3$ (77 %); e) CH_2=CHOEt, PPTS (96 %); f) H_2, 10 %Pd-C, AcOEt (96%); g) L-Selectride, THF, -78°C (94 %); h) CH_2=CHOEt, PPTS (98 %); i)n-Bu_4NF, THF (92 %); j) $(COCl)_2$, DMSO, CH_2Cl_2, -50°C then Et_3N (93 %); k) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, H_2O, t-BuOH (88 %); l) 2 %HCl, THF (93 %); m) PCC, AcONa, CH_2Cl_2(94 %)

ethyl acetals to give **4** and **5**,[13] in a ratio of 2.4 : 1, owing to the anomeric effect.[14]

Elaboration of the pyranone to the target bislactone was achieved as follows. Catalytic hydrogenation of **4** on 10 % Pd-C proceeded with high stereoselectivity (> 95 %) from the less hindered α-face to furnish the saturated compound (**6**), whose stereochemistry at the C-4 position was assumed to be S configuration based on its NMR spectrum and unambiguously determined by its conversion into the bislactone (**12**). Although sodium borohydride reduction of the ketone (**6**) gave a 1:1 mixture of the alcohols (**7**) and (**8**), treatment of **6** with L-Selectride in THF at -78°C afforded the desired **7** in 81 % yield, together with **8** in 13 % yield. After protection of the hydroxy group as its ethoxy ethyl ether, the resulting silyl ether was exposed on fluoride ion to give **9**. Oxidation of the alcohol (**9**) in two steps (sequential Swern oxidation[15] and sodium chlorite oxidation[16]) afforded the corresponding carboxylic acid (**10**). Acid treatment of **10** brought about

the deprotection of the ethoxy ethyl ether followed by the ring transformation to furnish the lactol (**11**), which was further oxidized to the bislactone (**12**), $[\alpha]_D^{25}$ -32.9°(EtOH) (lit.,[6b] $[\alpha]_D^{20}$ -33° (EtOH)). Its spectral data are identical with those reported.[5a,6b]

Having the bislactone in hands, we then turned our attention to the conversion of **11** into the key intermediate for the synthesis of (-)-canadensolide as follows (Scheme 2). Compound (**11**) was protected as the benzyl acetal to give the lactone, which was subjected to reduction with diisobutylaluminum hydride followed by acetalization of the lactol with ethyl vinyl ether to give **13**. After deprotection of the benzyl acetal, the corresponding lactol was oxidized to the known lactone (**14**).[6b] Since **14** was converted into **1**, this constitutes a formal synthesis of (-)-canadensolide.



Scheme 2. *Reagents*: a) BnOH, p-TsOH, CH_2Cl_2 (79 %); b) DIBAL, THF, -78°C (87 %); c) CH_2=CHOEt, PPTS (83 %); d) H_2, $Pd(OH)_2$, EtOH (78 %); e) PCC, AcONa, CH_2Cl_2 (74 %)

In summary, we have developed a new enantioselective method for the construction of the canadensolide-type bislactone starting from the chiral furylcarbinol bearing suitable functionalities. This method would be applicable to the syntheses of other types of antifungal bislactones such as avenaciolide and isoavenaciolide.

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9. All new compounds were fully characterized by 270 MHz ^{1}H-NMR, IR, and high resolution mass spectroscopy. The spectral and physical data of selected compounds are as follows.
(R)-3: $[\alpha]_D^{25}$ +9.6° (c 2.0, $CHCl_3$). ^{1}H-NMR($CDCl_3$) 0.11(6H, s, $SiMe_2$), 0.90(3H, d, J=6.7 Hz, Me), 0.92(9H, s, t-Bu), 1.24-1.43(4H, m, CH_2X2), 1.87(2H, q, J=6.7 Hz, CH_2), 4.62(2H, s, CH_2O), 4.74(1H, t, J=6.7 Hz, CHOH), 6.28(1H, d, J=1.8 Hz, 4-H), 7.27(1H, d, J=1.8 Hz, 5-H).
4: ^{1}H-NMR($CDCl_3$) 0.08(6H, s, $SiMe_2$), 0.91(3H, t, J=6.1 Hz, Me), 0.92(9H, s, t-Bu), 1.20-1.45(10H, m, MeX2 and CH_2X2), 1.60-1.70 and 1.90-2.00 (each 1H, each m, CH_2), 3.47-3.87(2H, m, OCH_2), 4.36 and 4.46(each 0.5H, each dd, J=7.9 and 3.7 Hz, 2-H), 4.37(2H, d, J=1.8 Hz, CH_2O), 4.96 and 5.03(each 0.5H, each q, J=5.5 Hz, OCH), 5.55-5.62(1H, m, 6-H), 6.77 and 6.84(each 0.5H, each dt, J=3.7 and 1.8 Hz, 5-H).
7: ^{1}H-NMR($CDCl_3$) 0.07(6H, s, $SiMe_2$), 0.90((9H, s, t-Bu), 0.92(3H, t, J=6.7 Hz, Me), 1.21 and 1.22(each 1.5H, each t, J=7.3 Hz, Me), 1.25-1.70 (13H, m, 4-H, 5-H_2, CH_2X2, and MeX2), 1.85-2.05(2H, m, CH_2), 3.40-4.00(6H, m, 2-H, 3-H, CH_2OSi, and OCH_2), 4.84 and 4.93(each 0.5H, each q, J=5.5 Hz, OCH), 5.02 and 5.11(each 0.5H, each t, J=4.3 Hz, 6-H).
12: ^{1}H-NMR($CDCl_3$) 0.94(3H, t, J=6.7 Hz, Me), 1.38-1.60(4H, m, CH_2X2), 1.78-2.00(2H, m, CH_2), 2.93(2H, d, J=6.1 Hz, 1-H_2), 3.51(1H, q, J=6.1 Hz, 2-H), 4,59(1H, ddd, J=7.9, 6.7, and 3.7 Hz, 4-H), 5.11(1H, dd, J=6.1 and 3.7 Hz, 3-H).
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