Tetrahedron Letters,Vol 23,No.49,pp 5185-5188,1982 0040-4039/82/495185-04$03.00/0
Printed in Great Britain

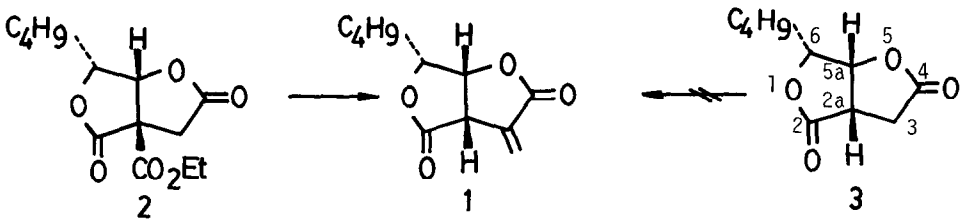
AN EFFICIENT SYNTHESIS OF BISLACTONE SKELETON LEADING TO *d,l*-CANADENSOLIDE[1]

Takashi Sakai, Masanori Yoshida, Shoichi Kohmoto,
Masanori Utaka, and Akira Takeda*
Department of Synthetic Chemistry, School of Engineering,
Okayama University, Tsushima, Okayama 700, Japan

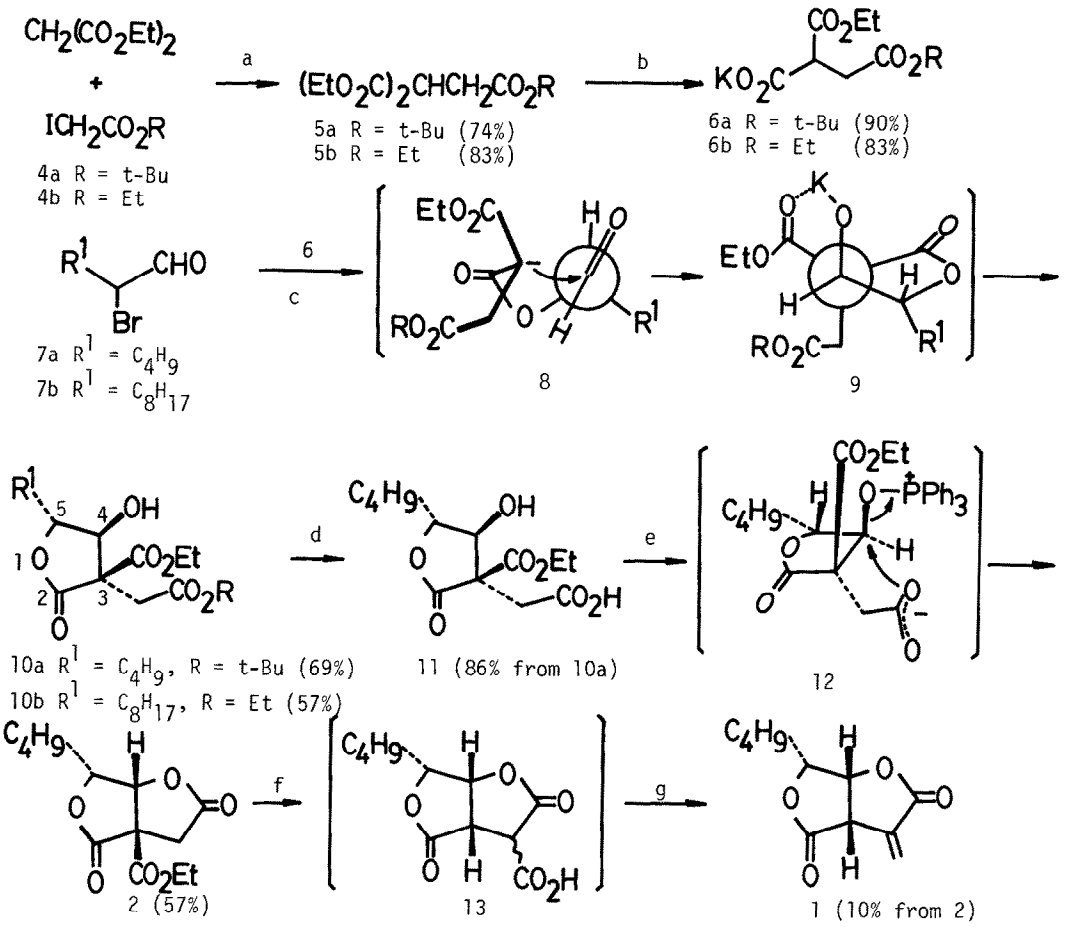
Abstract A novel, stereoselective total synthesis of *d,l*-canadensolide by application of the two-phase reaction (Bu_4NBr, benzene-H_2O) of 2-bromohexanal with 1,1,2-ethanetricarboxylic acid 2-*tert*-butyl, 1-ethyl ester, 1-potassium salt (6a) is described

A series of antifungal mold metabolites such as avenaciolide,[2] isoavenaciolide,[3] ethitholide,[3a] and canadensolide (1)[4,5,6] have attracted much attention owing to unique bis-γ-lactone skeletons as well as biological activities In exploring synthetic methods of these substances, considerable efforts have been concentrated on the methodology of the stereoselective construction of required skeletons and the introduction of exo-methylene group We previously reported an efficient synthesis of *d,l*-avenaciolide by applying the two-phase reaction (Bu_4NBr, benzene-H_2O) of α-halo aldehyde with potassium ethyl malonate [7] As a part of our successive reserches[7,8] on the effective application of this method, we report here a novel, stereoselective total synthesis of *d,l*-canadensolide (1)

In the synthetic studies of 1 reported so far,[6,9] attempts to introduce an exo-methylene group to bislactone 3 were unsuccessfull, in contrast to the successful introduction in the case of avenaciolide bislactone skeleton [10] The results can be explained by the facile deprotonation at C_{2a} under a variety of basic conditions We solved this problem by using the bislactone 2, which possesses ethoxycarbonyl group at the C_{2a}-position, as the key intermediate for 1 The compound 2 was elaborated stereoselectively *via* the two-phase reaction system (Sheme I)



Scheme I



(a) 1 equiv Bu_4NHSO_4, 2 equiv NaOH, CH_2Cl_2-H_2O (1 1), (b) 1 equiv KOH, EtOH, (c) 0 1 equiv Bu_4NBr (TBAB), benzene-H_2O (1 1), (d) CF_3CO_2H, (e) 1 equiv PPh_3, 1 equiv $EtO_2CN{=}NCO_2Et$ (DEAD), THF, (f) 6 2 equiv $CH_3OMgOCO_2CH_3$ (2 M solution in DMF), (g) 1 48 equiv NaOAc-AcOH, excess of 37% aqueous HCHO and Et_2NH

Monopotassium tricarboxylates (6a and 6b) were obtained readily by hydrolysis (ethanolic KOH)[11] of 1,1,2-ethanetricarboxylic esters (5a and 5b), which were prepared by the two-phase reaction (Bu_4NHSO_4, NaOH, CH_2Cl_2-H_2O)[12] of ethyl malonate with iodoacetic ester (4a or 4b)

The two-phase system consisting of 2-bromohexanal (1 mol), carboxylate 6a (1 mol), and Bu_4NBr (0 1 mol) in benzene-H_2O (1 1) was stirred vigorously for 40 h at reflux temperature to give β-hydroxy-γ-lactone 10a,[13] stereoselectively In a similar way, C_5-octyl analog 10b[13] was obtained The relative stereochemistries of C_5-alkyl and C_4-hydroxyl group, and of the hydroxyl group and C_3-acetate moiety are confirmed to be trans by consideration of the reaction mechanism and by eventual

conversion of 10a into bislactone 2 The cyclization to γ-lactone 10 may preferentially occur in a manner as illustrated in the structure 8 to provide a more stable six-membered chelate ring structure (9)

Chemospecific hydrolysis (CF_3CO_2H, room temperature, 3 h) of *tert*-butyl ester of the lactone 10a afforded the corresponding acid lactone 11,[13] mp 88-90 °C The compound 11 did not cyclize to bislactone 2 even by treating with refluxing CF_3CO_2H This fact also imply that the relative stereochemistry of C_4-hydroxyl and C_3-acetate moiety of 11 is trans and suggests that intramolecular S_N2-type lactonization is promising

Hence, the lactone 11 was allowed to react with PPh_3 and diethyl azodicarboxylate (DEAD) (THF, room temperature, overnight) by the adaptation of Mitsunobu's method [14] The resulting product was separated by column chromatography (silica gel, pentane-ether 2 1) to give bislactone 2[13,15] with the desired stereochemistry In the ^1H NMR spectrum of 2, the coupling constant due to C_{5a}-H (δ 5 08, d) and C_6-H (δ 4 76, dt) is 4 Hz, which suggests that the relative stereochemistry of these protons is the required cis configuration [5,16]

Finally, the introduction of exo-methylene group was accomplished by Johnson's procedure [10] The bislactone 2 was heated with a 2 M solution of magnesium methyl carbonate (MMC) in DMF at 120 °C for 3 h to afford carboxylated compound 13 It was subjected to the Mannich condensation to give *d,l*-canadensolide 1 One recrystallization (CCl_4) subsequent to TLC (Merck, Kieselgel 60 F_{254}, hexane-ether 1 2, R_f 0 33-0 45) afforded 1[17] in 10% yield, mp 96-96 5 °C (lit [5c] 96-96 5 °C)

Acknowledgement This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture in Japan (Grant No 57470067)

References and Notes

1 Presented in part at the 45th Annual Meeting of the Chemical Society of Japan, Tokyo, Abstr II, p 933 (1982)

2 a) D Brooks, B K Tidd, and W B Turner, J Chem Soc , 1963, 5383, b) J J Ellis, F H Stodola, R F Vesonder, and C A Glass, Nature, 203, 1382

3 a) D C Aldrige and W B Turner, J Chem Soc , C, 1971, 2431, b) R C Anderson and B Fraser-Reid, Tetrahedron Lett , 1977, 2865

4 Isolation N J McCorkindale, J L C Wright, P C Brian, S M Clarke, and S A Hutchinson, Tetrahedron Lett , 1968, 727

5 Synthesis of racemic canadensolide a) M Kato, M Kageyama, R Tanaka, K Kuwahara, A Yoshikoshi, J Org Chem , 1975, 40, 1932, b) M Utaka, H Fujii, M Iwamoto, M Meguro, S Tsuboi, and A Takeda, the 37th Annual Meeting of the Chemical Society of Japan, Sendai, Abstract II, p 853 (1978) c) Non-

stereoselective synthesis R M Carlson and A R Oyler, J Org Chem , 1976, 41, 4065

6 Synthesis of (-)-canadensolide a) R C Anderson and B Fraser-Reid, Tetrahedron Lett , 1978, 3233, b) H Ohrui, N Sueda, and H Kuzuhara, Nippon Kagaku Kaishi, 1981, 769

7 T Sakai, H Horikawa, and A Takeda, J Org Chem., 1980, 45, 2040

8 T Sakai, K Seko, A Tsuji, M Utaka, and A Takeda, J Org Chem , 1982, 47, 1101

9 H Kosugi, S Sekiguchi, R Sekita, and H Uda, Bull Chem Soc Jpn , 1976, 49, 520

10 W L Parker and F Johnson, J Am Chem Soc , 1969, 91, 2708, W L Parker and F Johnson, J Org Chem , 1973, 38, 2489

11 R E Strube, Org Syntheses, Coll Voll IV, Willey, New York, 1963, p 417

12 A Brandstrom and U Junggren, Tetrahedron Lett , 1972, 473

13 All of new compounds obtained in this work gave acceptable elemental analysis Spectroscopic data (IR and ^{1}H NMR) for typical products are as follows

9a IR (neat) 1776, 1739, 1728 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 0 75-2 10 (m, 9, C_4H_9), 1 30 (t, 3, J = 7 Hz, ester CH_3), 1 50 [s, 9, $C(CH_3)_3$], 2 50 (d, 1, J = 17 Hz, C_α H), 3 20 (d, 1, J = 17 Hz, C_α H), 4 30 (q, 2, J = 7 Hz, ester CH_2), 4 15-4 60 (m, 3, C_4 H, C_5 H, and OH)

10 IR (KBr) 3600-2500, 1765, 1740 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 0 60-2 00 (m, 9, C_4H_9), 1 29 (t, 3, J = 7 Hz, ester CH_3), 2 69 (d, 1, J = 18 Hz, C_α H), 3 32 (d, 1, J = 18 Hz, C_α H), 4 29 (q, 2, J = 7 Hz, ester CH_2), 4 00-4 70 (m, 2, C_4 H, C_5 H), 5 8-6 6 (br s, 2, OH and CO_2H)

2 IR (neat) 1790 and 1741 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 0 70-2 20 (m, 9, C_4H_9), 1 32 (t, 3, J = 7 Hz, ester CH_3), 3.01 (d, 1, J = 18 Hz, C_3 H), 3 43 (d, 1, J = 18 Hz, C_3 H), 4 31 (q, 2, J = 7 Hz, ester CH_2), 4 76 (dt, 1, J = 4 Hz and 7 Hz, C_6 H), 5 08 (d, 1, J = 4 Hz, C_{5a} H)

^{13}C NMR spectra also supported these structures

14 O Mitsunobu and M Eguchi, Bull Chem Soc Jap , 1971, 44, 3427

15 The structure was identified by comparison of the spectral data with those of the corresponding methyl ester prepared by the independent synthesis S Tsuboi, H Fujita, K Muranaka, and A Takeda, the 44th Annual Meeting of the Chemical Society of Japan, Okayama, Abstract III, p 510 (1981)

16. T Mukaiyama, K Hagino, H Takei, and K Saigo, Bull Chem Soc Jpn , 1971, 44, 3427

17. Spectral data (IR and ^{1}H NMR) were identical with those of the literature (see ref 5a and 5c)

(Received in Japan 23 August 1982)