Pergamon

Tetrahedron Letters, Vol. 36, No. 28, pp. 5035-5036, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00915-9

A Synthetic Approach to (+)-Brefeldin A

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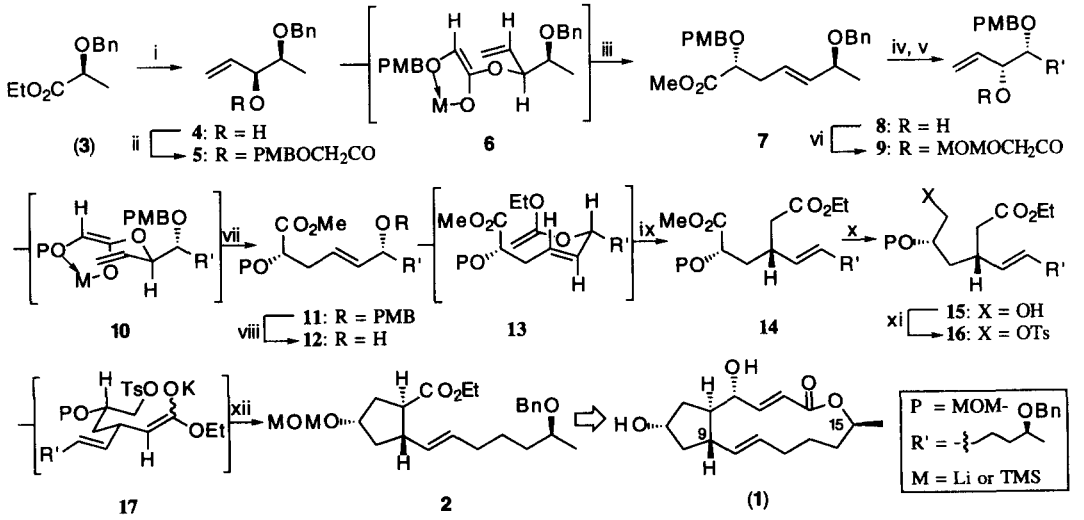
Abstract: A unique 12-step scheme for the stereoselective synthesis of (+)-brefeldin A intermediate **2** starting from ethyl O-benzyl (S)-lactate (**3**) has been accomplished.

The unusually broad spectrum of biological activity exhibited by (+)-brefeldin A (**1**), a thirteen-membered macrocyclic fungal metabolite, has prompted rather impressive synthetic efforts to date in a number of laboratories.[1] Described herein is a new stereoselective approach to an advanced intermediate **2** for the synthesis of (+)-brefeldin A (**1**), which is unique in the sense that the chirality of ethyl O-benzyl (S)-lactate (**3**) [C_{15} in the brefeldin numbering system] controls the relative stereochemistry of the rest of remote stereogenic centers in **2**. Our synthetic scheme features 1) iterative 1,4-chirality transfer processes by 'chelation-controlled' Ireland ester enolate Claisen rearrangements [**5** → **7** & **9** → **11**][2]; 2) consecutive Ireland-Johnson [3,3]-sigmatropic rearrangements [**9** → **11** & **12** → **14**]; 3) a chemoselective $NaBH_4$ reduction of α-alkoxy ester function in the presence of an ordinary ester [**14** → **15**]; 4) a stereoselective intramolecular ester enolate alkylation [**16** → **17**] as key steps as summarized in the following scheme.



Reagents: i) a) DIBALH, -78 °C, 1.5 h b) CH_2=$CHMgBr$, ether, -78 °C to rt, 2 h (73%); ii) $PMBOCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, rt, 4 h (97%); iii) a) LDA, TMSCl, TEA, THF, -78 °C to rt, 2 h b) CH_2N_2, ether, rt, 30 min (85%); iv) NH_2NH_2, CuO, THF, NaOAc, reflux, 6 h (60%); v) a) DIBALH, -78 °C, 1.5 h b) CH_2=$CHMgBr$, ether, -78 °C to rt, 2 h (5.7 : 1; 73%); vi) $MOMOCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, rt, 3 h (93%); vii) a) LDA, TMSCl, TEA, THF, -78 °C to rt, 2 h b) CH_2N_2, ether, rt, 30 min (86%); viii) DDQ, CH_2Cl_2-H_2O (18 : 1), rt, 30 min (86%); ix) $CH_3C(OEt)_3$, phenol (cat), 120 °C, 4 h (84%); x) $NaBH_4$, EtOH, rt, 3 h (97%); xi) TsCl, pyridine, $CHCl_3$, rt, 24 h (93%); xii) KHMDS, THF, -78 °C, 30 min, then rt, 30 min (56%).

Thus, readily available ethyl O-benzyl (S)-lactate (**3**)[3] was converted to *syn*-1,2-diol (6:1 *syn/anti* ratio) derivative **4** by successive treatment with vinylmagnesium bromide in ether according to Burke's one-pot protocol[4] in 85% yield.[5,6] Acylation of allylic alcohol **4** with $PMBOCH_2CO_2H$ under Hassner's conditions[7] produced allylic glycolate **5**, which was subjected to the Burke-Fujisawa-Kallmerten 'chelation-controlled' modification[8] of the Ireland Claisen rearrangement to furnish γ, δ-unsaturated glycolate **7** in a highly stereoselective manner, by a 1,4-chirality transfer process as shown in **6** (67% overall yield for two steps). After the removal of the superfluous double bond in compound **7** by a diimide reduction, the resulting ester **8** was converted to the more highly elaborated γ, δ-unsaturated glycolate **11** by a reiterative three-step sequence in comparable overall yield and stereoselectivity.[5,6] Deprotection of the PMB group of compound **11** with DDQ using Yonemitsu's conditions[9] generated secondary allylic alcohol **12**, which underwent a smooth Johnson orthoester Claisen rearrangement[10] with triethyl orthoacetate to give the corresponding diester **14** via transition state geometry **13**. Chemoselective $NaBH_4$ reduction of the α-alkoxy ester function of **13** in EtOH at room temperature, followed by tosylation, afforded the requisite internal alkylation substrate **16** in 90% overall yield for the two steps. Finally, the crucial cyclization of ω-tosyl ester **16** with KHMDS in THF provided the desired cyclopentanecarboxylate **2** in 56% yield.[11] The racemic debenzylated methyl ester corresponding to **2** has been previously converted to (±)-brefeldin A by Bartlett.[12]

In summary, a novel and efficient stereoselective sequence for preparing synthetic intermediate **2** for total synthesis of (+)-brefeldin A has been developed using 1,3- and 1,4-chirality transfer processes involving iterative, consecutive [3,3]-sigmatropic rearrangements, in addition to an internal ester enolate alkylation.

Acknowledgments: We acknowledge financial support from the OCRC and KMOE (BSRI-94-3420).

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5. All new compounds exhibited satisfactory spectroscopic data. The ratio of stereoisomers was determined by capillary g. l. c. analysis and/or rigorous analysis of high-field ^1H NMR spectra. Compound **2**: **IR** (neat) ν 1730 cm^{-1}; **^1H NMR** ($CDCl_3$, 400 MHz) δ 1.11 (d, J = 5.6 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H), 1.25 - 1.55 (m, 6H), 1.91 (q, J = 6.4 Hz, 2H), 1.96 (m, 2H), 2.21 (m, 1H), 2.58 (m, 1H), 3.28 (s, 3H), 3.42 (m, 1H), 4.05 (dq, J = 2.4, 7.2 Hz, 2H), 4.24 (m, 1H), 4.38 (d, J = 12 Hz, 1H), 4.49 (d, J = 12 Hz, 1H), 4.56 (s, 2H), 5.25 - 5.43 (m, 2H), 7.25 - 7.30 (m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 14.3, 19.6, 25.3, 32.4, 36.1, 36.9, 40.0, 45.7, 48.7, 55.3, 60.3, 70.3, 74.7, 77.1, 95.3, 127.3, 127.6, 128.3, 130.7, 132.2, 139.1, 175.3; **HRMS** calcd for $C_{24}H_{36}O_5(M^+)$ 404.2563, found 404.2541; $[\alpha]^{20}_D$ -19.2 (c = 0.13, CH_3OH).
6. The stereoselectivity of **4** can be improved (66.4:1) if the ester (**3**) is first reduced with DIBALH to the corresponding aldehyde, followed by addition of CH_2=CHMgBr in the presence of $MgBr_2$. Furthermore, the stereoselectivity of **8** is nearly complete using this two-step procedure.
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(*Received in Japan* 6 *March* 1995; *revised* 1 *May* 1995; *accepted* 18 *May* 1995)