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FACILE SYNTHESIS OF (+)-BREFELDIN A[1)]

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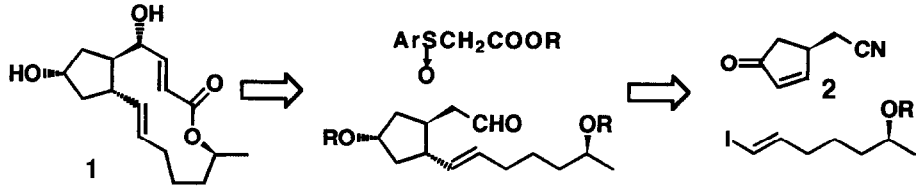
(+)-Brefeldin A (**1**) was synthesized by using (+)-4-cyanomethylcyclopent-2-en-1-one (**2**) as a key compound. 4-Hydroxy-2-enoate functionality was built by the reaction of the aldehyde (**7**) with (S)-ethyl p-chlorophenylsulfinylacetate.

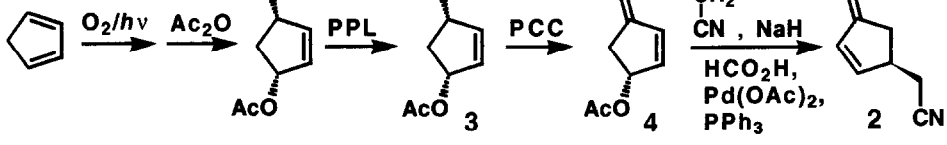
Brefeldin A (**1**) seems to be one of attractive compounds in a synthetic point of view because of its structural and biological interests.[2)] It has five asymmetric carbons in the bicyclo[13.3.0]hexadecadienoate skeleton and exhibits a wide range of biological activity including antibiotic, cytostatic, antimitotic and antiviral effects.[2c)] Here we show a facile synthesis of the optically active brefeldin A based on the retrosynthetic study as shown in Scheme 1.[3)]



Scheme 1

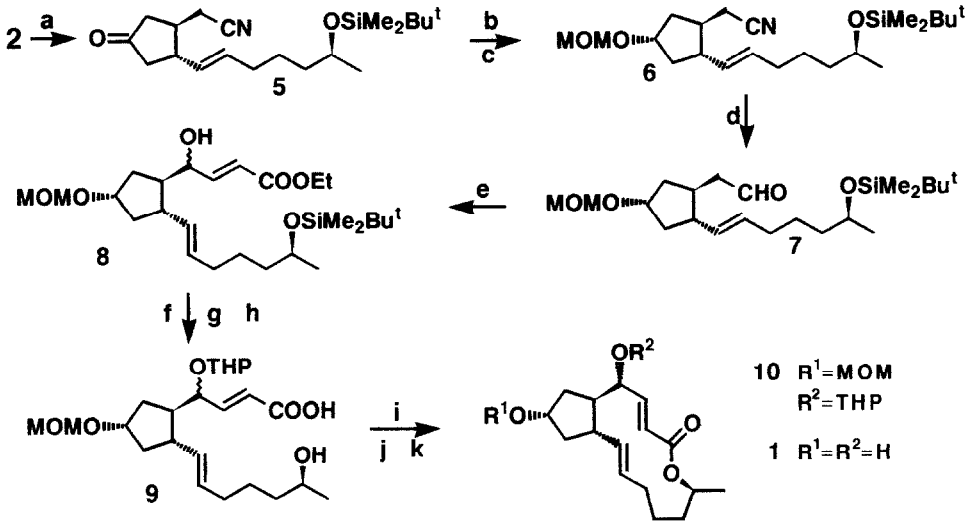
Our synthetic strategy is characterized by the following points which were recently developed by us; 1) the new optically active compound, (+)-4-cyanomethylcyclopent-2-en-1-one (**2**), was used effectively as an aldehyde synthon and 2) the reaction of sulfinyl-activated methylene compound with aldehyde was effectively employed to form γ-hydroxy-αβ-unsaturated ester funtionality.[4)]

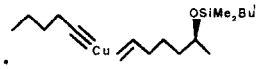
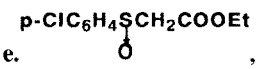
(+)-4-Cyanomethylcyclopent-2-en-1-one (**2**) was prepared as shown in scheme 2. 1,4-Diacetoxycyclopent-2-ene, derived by the photo-oxidation of cyclopentadiene to 1,4-dihydroxycyclopent-2-ene and followed by acetylation, was selectively hydrolyzed by using lipase (Sigma Type II; porcine pancreas) in phosphate buffer(pH 7)-acetone solution to optically active hydroxy acetate **3**.[5)] PCC oxidation of the hydroxy acetate **3** afforded (+)-4-acetoxycyclopent-2-en-1-one (**4**) (88%, $[\alpha]_D$+110° (c 1, $CHCl_3$)), which was converted to the key intermediate **2** as follows.



Scheme 2

To a stirring THF suspension of NaH (1.1 equiv) was added a THF solution of allyl cyanoacetate (1.1 equiv) and then **4** succesively at -40 °C and the stirring was continued for 30 min. To the reaction mixture, formic acid (3 equiv) was added at -20 °C and then $Pd(OAc)_2$ (5 mol%) and triphenylphosphine (10 mol%) were added at room temperature, and the mixture was stirred for additional 3 hours at 40 °C[6] to give (+)-4-cyanomethyl-cyclopent-2-en-1-one (**2**).[7]



a.  **11**, b. K selectride, c. MOM-Cl/Et_2NH, d. DIBAH, e.  , f. DHP/H^+, g. LiOH, H^+, h. Et_4NF, i. 2,4,6-trichlorobenzoylchloride/Et_3N/DMAP, j. H^+, k. $TiCl_4$.

Scheme 3

Treatment of **2** with cuprate **11**[8] gave the 1,4-adduct **5** in 65% yield. The 3,4-disubstituted cyclopentanone **5** was reduced to alcohol stereoselectively by reduction with K-selectride at -80 °C, and the produced hydroxy group was protected by treatment with methoxymethyl chloride to MOM-ether, and the desired product **6** was obtained in 60% yield after column chromatography on silica gel.[9] Conversion of nitrile to aldehyde was carried out by treatment with diisobutylaluminum hydride(DIBAH), and the aldehyde **7** was condenced with the sulfoxide (-)-(S)-ethyl p-chloro-phenylsulfinylacetate in the presence of piperidine to give γ-hydroxy-αβ-unsaturated ester **8**[10] in 81% yield based on **6**. After protection of the hydroxy group of **8** as THP-ether, both the ethyl ester and the dimethyl-t-butylsilyl ether functionalities of the THP-ether were hydrolyzed to give hydroxy carboxylic acid **9** by hydrolysis with lithium hydroxide and tetraethylammonium fluoride respectively. Treatment of **9** with 2,4,6-trichlorobenzoyl chloride and triethylamine in dry THF at room temperature and then with 4-dimethylaminopyridine (DMAP) in refluxing dry toluene[2j] gave **10** in 80% yield based on **8**. Acid hydrolysis of **10** with AcOH-THF-H_2O(3:1:3) at 50 °C gave diastereoisomeric mixture in the ratio of ca. 3:1, and the major product was separated and treated with titanium tetrachloride to give (+)-brefeldin A ($[\alpha]_D$ +95° (c 0.14, methanol))[11] in 63% yield.

Through our synthetic study on brefeldin A described here, it has been clear that 1) new optically active compound (+)-4-cyanomethylcyclopent-2-en-1-one (**2**) is prepared easily and employed for synthesis of 3,4-disubstituted cyclopentanone derivative and 2) (S)-ethyl p-chlorophenylsulfinylacetate reacts with aldehyde in the presence of piperidine to give S conformational allylic alcohol predominantly as expected.[10)]

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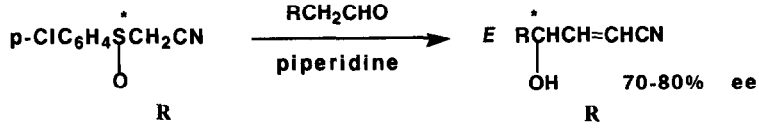
References

1) This study has been presented; J. Nokami et al., the 33rd TEAC meeting, Sendai (September), Abstract pp 301-302(1989) and the 60th annual meeting (Chem. Soc. Jpn), Hiroshima (October) Abstract I 2B1-14(1990).

2) Synthetic studies on (+)-brefeldin A: (a) T. Kitahara, K. Mori, M. Matsui, *Tetrahedron Lett.*, 3021(1979); (b) A. E. Greene, C. L. Drian, P. Crabbe', *J. Am. Chem. Soc.*, **102**, 7584(1980); (c) C. L. Drian, A. E. Greene, *J. Am. Chem. Soc.*, **104**, 5473(1982); (d) B. M. Trost, J. Lynch, P. Renaut, D. H. Steinman, *J. Am. Chem. Soc.*, **108**, 284(1986); (±)-brefeldin A: (e) E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614(1974); (f) E. J. Corey, K. C. Nicolaou, L. S. Melvin, Jr., *ibid.*, **97**, 654(1975); (g) E. J. Corey, R. H. Wollenberg, *Tetrahedron Lett.*, 4701,4705(1976); (h) E. J. Corey. R. H. Wollenberg, D. R. Williams, *ibid.*, 2243(1977); (i) P. A. Bartlett, F. R. Green III, *J. Am. Chem. Soc.*, **100**, 4858(1978); (j) M. Honda, K. Hirata, H.Sueoka, T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.*, **22**, 2679(1981); (k) K. Nakatani, S. Isoe, *ibid.*, **26**, 2209(1985); (+)-brefeldin C: (l) S. L. Schreiber, H. V. Mayers, *J. Am. Chem. Soc.*, **110**, 5198(1988).

3) The latest synthesis which based on the same concept as we described here has been reported; E. J. Corey and P. Carpino, *Tetrahedron Lett.*, **31**, 7555(1990).

4) (a) Reaction of α-(phenylsulfinyl)acetonitrile with ketone or aldehyde to γ-hydroxy-αβ-unsaturatednitrile and its synthetic application has been reported by us: J. Nokami, T. Mandai, Y. Imakura, K. Nishiuchi, M. Kawada, S. Wakabayashi, *Tetrahedron Lett.*, 4489(1981); T. Ono, T. Tamaoka, Y. Yuasa, T. Matsuda, J. Nokami, S. Wakabayashi, *J. Am. Chem. Soc.*, **106**, 7890(1984). (b) Reaction of optically active sulfoxide with aldehydes to optically active alcohols has also been reported: J. Nokami, T. Mandai, A. Nishimura, T. Takeda, S. Wakabayashi, *Tetrahedron Lett.*, **27**, 5109(1986).



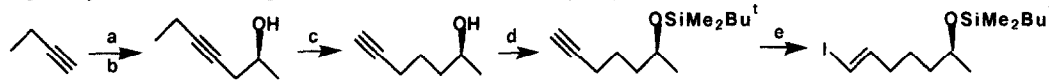
(c) Similar reaction of methyl α-(p-chlorophenylsulfinyl)acetate with aldehydes was employed for synthesis of methyl γ-hydroxyalkenoates: R. Tanikaga, Y. Nozaki, T. Tamura, A. Kaji, *Synthesis*, 134(1983).

5) Typical procedure is representative as follows. To a suspension of lipase (Sigma Type II, crude (steapsin) from porcine pancreas, 22g) in phosphate buffer(pH 7)-acetone (1/1(v/v); 122 ml), cis 1,4-diacetoxycyclopent-2-ene (1.5 g) was added and the mixture was stirred for 3-5 days at room temperarture. After filtration of the reaction mixture, the filtrate was concentrated to remove acetone and the residual oil was extracted with ethyl acetate. (1R,4S)-1-Acetoxy-4-hydroxycyclopent-2-ene (**3**), $[\alpha]_D$ +65° (c 1.0, $CHCl_3$)) was obtained in 60% yield and the diacetate was recovered (20%) after column chromatography on silica gel. Similar enzymatic hydrolysis of cis 1,4-diacetoxy-cyclopent-2-ene to (1R,4S)-**3** by using porcine pancreatic lipase (PPL; Fluka 62300) has been reported; K. Lauman, M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1298(1986).

6) Allyl malonate-derivatives and allyl cyanoacetate-derivatives are hydrolyzed (to acid) and decarboxylated succesively to the corresponding monoesters, monocarboxylic acids, and nitriles by palladium-catalyzed reaction with HCOOH-Et_3N. These reactions required several hours (over than 10 hours for nitrile) in refluxing dioxane; T. Mandai, M. Imaji, H. Takada, M. Kawata, J. Nokami, J. Tsuji, *J. Org. Chem.*, **54**, 5395 (1989). However, in this case, it takes only few hours at 40 °C.

7) 87% yield, $[\alpha]_D$+147° (c 1, $CHCl_3$). IR 2230, 1715, 1665, 1590 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.13(1H, dd, J=2.4 and 18.8 Hz), 2.62(2H, d, J=6.6 Hz), 2.71(1H, dd, J=6.6 and 18.8 Hz), 3.4(1H, m), 6.34(1H, dd, J=2.0 and 5.6), 7.63(1H, dd, J=2.4 and 5.9 Hz). ^{13}C-NMR($CDCl_3$) δ 22.3(t), 37.3(t), 39.8(d), 116.9(s), 136.2(d), 162.8(d), 206.4(s).

8) Optically active side chain precursor was derived from (-)-propylene oxide (Aldrich, 99%) as shown below.



90% ($[\alpha]_D$+14.2°) 68% ($[\alpha]_D$+13.6°) 95% ($[\alpha]_D$+11.2°) 76% ($[\alpha]_D$+8.5°)

a. n-BuLi, -40-0 °C, THF; b.  **/HMPA, -20-0 °C; c. KH/$NH_2CH_2CH_2NH_2$;**

d. Me_2Bu^tSiCl/imidazole; e. Cp_2ZrCl_2/NaAl($OCH_2CH_2OCH_3)_2H_2/I_2$

9) Stereoselectivity was found to be ca. 3/1(α/β) by the reduction with either K-selectride or L-selectride, though no selectivity was found by $NaBH_4$ reduction.

10) Our previous investigation on the reaction of optically active sulfinyl-activated methylene compound suggests that the S conformational sulfoxide should give S allylic alcohol ref 4b.

11) Optical rotation of (+)-brefeldin A, $[\alpha]_D$+93° (c 2, methanol), was reported in ref 2c.

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