past the allylic centers of the smaller ring. Further studies will be directed at this point. Interestingly, none of the three "jump rope" betweenanenes **13a–c** gives rise to a colored charge-transfer complex with tetracyanoethylene whereas the cis counterparts **12a–c** form deeply colored complexes.[23] Thus, in even the largest, most flexible betweenanene, **13c**, the double bond is not readily accessible to a bulky reagent.

(23) Merrifield, R. E.; Phillips, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 2778–2782.

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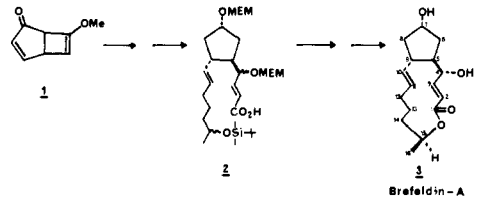
An Efficient Total Synthesis of (±)-Brefeldin-A[1]

Sir:

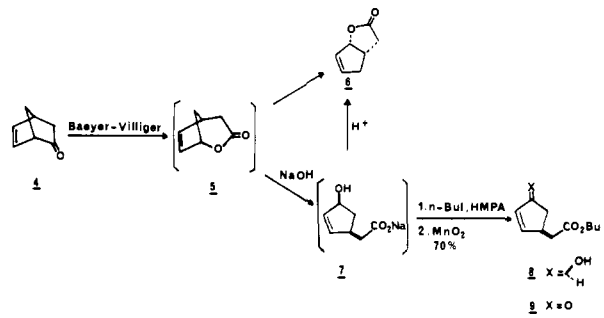
The unusually broad spectrum of biological activity exhibited by brefeldin-A (**3**)[2] combined with its structural resemblance to the prostaglandins has engendered a rather impressive synthetic effort to date in a number of laboratories.[3] In 1977 we reported[3b] a formal total synthesis of this fungal metabolite consisting of a high-yield conversion of the α-tropolone methyl ether photoproduct **1** to the monocyclic intermediate **2**, which had earlier[3a] been



transformed to racemic brefeldin-A. In this communication, we report a different total synthesis of this natural product that is substantially simpler, shorter, and more efficient than our original approach. The salient features of this synthesis include (a) ready access to an alternative Michael acceptor (replacing **1**), the "correct" enantiomer of which can be obtained through chiral induction as well as by resolution, (b) a streamlined construction of the problematic C-1 to C-4 portion of the molecule, and (c) an effective combination of protecting groups that permits easy differentiation at the C-1, -4, -7, and -15 functions (while still affording stereocontrol at C-4[3a–d]) and simplifies both chromatographic purifications and spectral analyses.

In reconsidering our earlier approach, we felt an important new objective to be a simple means of obtaining large amounts of a cyclopentenone that could be used as the Michael acceptor of the C-10 to C-16 portion of brefeldin-A and ultimately secured in the correct optically active form. We had already found that 6-heptyn-2-one is reduced with baker's yeast to (*S*)-(+)-6-heptyn-2-ol (to be used for the C-10 to C-16 portion) in up to 53% yield (5–10-g scale) and with virtually complete enantioselectivity.

Norbornenone (**4**) thus appeared to be an excellent starting



material—obtainable in optically active form[4–6] and, in principle, easily converted to a 4-[(carbalkoxy)methyl]cyclopentenone.[6a] Under the usual Baeyer–Villiger conditions, the product initially formed from norbornenone, lactone **5**, rearranged very readily to give the unwanted lactone **6**;[7] however, by using H_2O_2–NaOH in H_2O–Et_2O,[6b] lactone **5** could be intercepted to produce its hydroxy acid salt **7**, which in turn could be directly alkylated with excess *n*-butyl iodide in HMPA[8] at room temperature to afford the hydroxy ester **8** (racemic series). Allylic oxidation of **8** with manganese dioxide in chloroform then provided the desired enone ester **9** in 70% overall yield on large-scale runs.

Stereoselective conjugate addition to this cyclopentenone of the C-10 to C-16 carbon unit was carried out at −78 °C in THF by using the mixed cuprate **10**[3a,b] derived from the trans[9] vinyllithium reagent and (1-pentynyl)copper in the presence of 2 equiv of hexamethylphosphorous triamide[10] to give the trans adduct **11** in 72% yield after purification (Scheme I). A minor amount of the corresponding 5,9-cis product was also obtained (~4% yield). Reduction of the trans product **11** with L-Selectride in THF at −78 °C produced an ~2.7:1 mixture of the C-7 α- and β-alcohols,[11] from which the pure α-alcohol **12** could be conveniently separated in 65% yield from **11** through treatment with a catalytic amount of *p*-TsOH in refluxing toluene, followed by filtration over silica gel.[12] The C-7 hydroxyl group in **12** was then protected as the methyl ether (MeI, Ag_2O, CH_3CN, reflux,[14] 93%), which proved to be a very satisfactory alternative to the previously employed methoxyethoxymethyl and methoxymethyl C-7 hydroxyl protecting groups.[3a–d]

An improved sequence[15] for the construction of the requisite

(1) This synthesis was presented May 9, 1980, at SECO 17, Bordeaux, France.

(2) Singleton, V. L.; Bohonos, N.; Ullstrup, A. J. *Nature (London)* **1958**, *181*, 1072. Härri, E.; Loeffler, W.; Sigg, H. P.; Stähelin, H.; Tamm, Ch. *Helv. Chim. Acta* **1963**, *46*, 1235. Betina, V.; Nemec, P.; Kovâč, S.; Kjaer, A.; Shapiro, R. H. *Acta Chem. Scand.* **1965**, *19*, 519. Weber, H. P.; Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 2763 and references cited. For the biological effects of brefeldin-A, see footnotes 2–4 in ref 3c.

(3) (a) Corey, E. J.; Wollenberg, R. H. *Tetrahedron Lett.* **1976**, 4701, 4705. Corey, E. J.; Wollenberg, R. H.; Williams, D. R. *Ibid.* **1977**, 2243. (b) Baudouy, R.; Crabbé, P.; Greene, A. E.; Le Drian, C.; Orr, A. F. *Ibid.* **1977**, 2973. (c) Bartlett, P. A.; Green, F. R., III *J. Am. Chem. Soc.* **1978**, *100*, 4858. (d) Kitahara, T.; Mori, K.; Matsui, M. *Tetrahedron Lett.* **1979**, 3021. For other approaches, see: (e) Curran, D. P.; Scholtz, D. *Monatsh. Chem.* **1977**, *108*, 1401. (f) Livinghouse, T.; Stevens, R. V. *J. Chem. Soc., Chem. Commun.* **1978**, 754.

(4) Asymmetric induction in hydroboration: (a) Mislow, K.; Berger, J. G. *J. Am. Chem. Soc.* **1962**, *84*, 1956. (b) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1976**, *15*, 12. In Diels–Alder: (c) Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 6359. (d) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6909 and references cited.

(5) Resolution: Berson, J. A.; Walia, J. S.; Remanick, A.; Suzuki, S.; Reynolds-Warnoff, P.; Willner, D. *J. Am. Chem. Soc.* **1961**, *83*, 3986. Reference 4d.

(6) See also: (a) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397. (b) Weinshenker, N. W.; Stephenson, R. *J. Org. Chem.* **1972**, *37*, 3741.

(7) Meinwald, J.; Seidel, M. C.; Cadoff, B. C. *J. Am. Chem. Soc.* **1958**, *80*, 6303. The free acid corresponding to **7** was also very unstable, rearranging to **6**. See: Grieco, P. A.; Yokoyama, Y.; Withers, G. P.; Okuniewicz, F. J.; Wang, C.-L. J. *J. Org. Chem.* **1978**, *43*, 4178. See, however, ref 6.

(8) Shaw, J. E.; Kunerth, D. C.; Sherry, J. J. *Tetrahedron Lett.* **1973**, 689. The *n*-butyl ester was found to be the most satisfactory of the esters synthesized (Me, Et, *i*-Pr, *n*-Bu) in terms of ease of purification and degree of stereoselectivity in the subsequent conjugate addition reaction.

(9) Collins, P. W.; Jung, C. J.; Gasiecki, A.; Pappo, R. *Tetrahedron Lett.* **1978**, 3187.

(10) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(11) This mixture of alcohols could not be resolved into more than one spot on analytical TLC plates.

(12) The lactonized β-alcohol thus obtained (24% yield) could be converted to the α-alcohol **12** in 40% overall yield by successive treatment as follows: NaOH; CH_2N_2; DEAD, Ph_3P, AcOH;[13] NaOH, *n*-BuI, HMPA,[8] thus raising the yield of **12** from **11** to 75%.

(13) See ref 3c and references cited.

(14) See: Finch, N.; Fitt, J. J.; Hsu, I. H. S. *J. Org. Chem.* **1975**, *40*, 206 and references cited.

(15) Greene, A. E.; Le Drian, C.; Crabbé, P. *J. Org. Chem.* **1980**, *45*, 2713.

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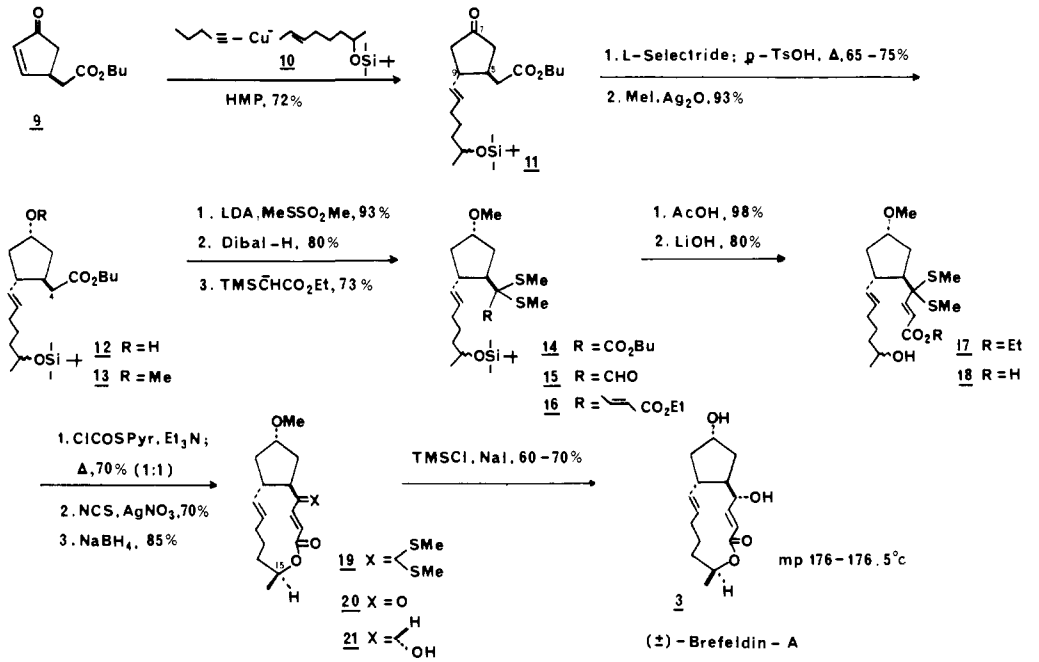
Scheme I



C-1 to C-4 γ-oxygenated crotonate unit commenced with bis(methylsulfenylation) of ester **13** (93% yield), which served to introduce directly a protected keto function at C-4, thereby avoiding the potential complications arising from the introduction of an additional center(s) of asymmetry at C-4. It is important to note that a *keto* function is ultimately "required" at C-4 in order to secure stereoselectively the C-4 α-OH of brefeldin-A (vide infra).[3a-d] Carefully controlled reduction of ester **14** with diisobutylaluminum hydride in toluene at ~−110 °C engendered aldehyde **15** directly and in high yield. As was the case with model compounds,[15] aldehyde **15** reacted only sluggishly with triethyl sodiophosphonoacetate; however, an alternative reagent, ethyl lithio(trimethylsilyl)acetate,[16] could again be employed successfully to produce the desired ketone-protected γ-oxocrotonate derivative **16**, exclusively *E*, in 73% yield. The C-15 hydroxyl group was selectively liberated by using aqueous acetic acid (98%), which was followed by saponification of the ethyl ester in aqueous ethanol to provide the hydroxy acid **18** in 80% yield.

Corey's double-activation process[17] was effective in lactonizing the hydroxy acid **18** and produced in 70% yield an ~1:1 mixture of diastereomeric lactones,[18] which were easily separated by silica gel chromatography (R_f 0.38, 0.48 using 30% Et_2O–pentane). The more polar isomer **19** was tentatively assigned the natural configuration at C-15, which proved ultimately to be correct.

The effectiveness of this particular choice for the C-4 and C-7 protecting groups can be seen by the simplicity of the conclusion of the synthesis. Treatment of **19** with silver nitrate and *N*-chlorosuccinimide in aqueous acetonitrile[19] at −10 °C afforded the fragile enone lactone **20** (70% yield), which, in the presence of sodium borohydride, was reduced at C-4 with virtually total stereoselectivity to give in high yield (±)-brefeldin-A 7-methyl ether (**21**). Exposure of this material to an excess of chlorotrimethylsilane and sodium iodide in acetonitrile[20] then concluded the synthesis, providing in 60–70% yield crystalline (±)-brefeldin-A, mp 176–176.5 °C (lit.[3c] racemic mp 175–175.5 °C), identified through spectral and chromatographic comparison with an authentic sample of the natural material. It is expected that this direct approach will prove useful for the synthesis of not only (+)-brefeldin-A (vide supra) but also various analogues of the natural product.[22]

Acknowledgment. We thank Dr. J. L. Luche for many helpful discussions, Dr. F. Seigle for advice on the microbial reduction, and Dr. H. P. Sigg and Dr. A. von Wartburg (Sandoz A. G., Basel) for samples of natural brefeldin-A. This work was supported by the CNRS.

(16) Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620. Hartzell, S. O.; Sullivan, D. F.; Rathke, M. W. *Tetrahedron Lett.* **1974**, 1463.

(17) Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, 2875 and references cited. Several other methods were examined in a closely related model system and were found to be much less effective.

(18) It is interesting to note that when this cyclization process is applied to the 4,7-bis(methoxyethoxymethyl) ethers, the derivative with the natural C-15 configuration lactonizes substantially more rapidly than that with the nonnatural configuration.[3a] In contrast, when Mukaiyama's procedure is used, the 4-dehydro compounds [7-(methoxymethyl) ethers] lactonize at roughly comparable rates,[3c] as in the present case.

(19) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(20) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247 and references cited.

(21) Department of Chemistry, University of Missouri, Columbia, MO 65211.

(22) **Note Added in Proof**: Another total synthesis of brefeldin-A has been reported: Köksal, Y.; Raddatz, P.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 472.

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Cyclopropane–Hydrogen Chloride Dimer: Identification and Geometry from Its Rotational Spectrum

Sir:

Recently we have reported a new method of observing the rotational spectra of weakly bound molecular complexes or otherwise transient molecules.[1] Weak molecular complexes are formed by collisional association in an adiabatic expansion of a high pressure gas through a nozzle into a vacuum. By flowing the complexes between the mirrors of a microwave Fabry–Perot cavity, the sensitive technique of pulsed Fourier transform microwave spectroscopy[2] can be used to observe the rotational

(1) T. J. Balle, E. J. Campbell, M. R. Keenan, and W. H. Flygare, *J. Chem. Phys.*, **71**, 2723 (1979); **72**, 922 (1980).

0002-7863/80/1502-7584$01.00/0