Highly Diastereoselective Conjugate Addition of Lithiated γ-Crotonolactone (But-2-en-4-olide) to Cyclic Enones To Give Syn-Adducts: Application to a Brefeldin Synthesis†

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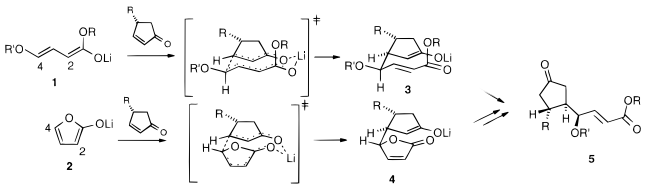
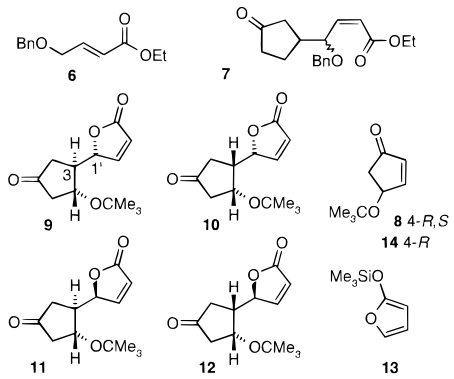
Lithiated allylic sulfoxides and phosphine oxides undergo diastereoselective conjugate addition to cyclic enones to provide vinylic products whose stereochemistry concisely relates to the geometry of the double bond in the starting allylic system.[1] From (*E*)-allylic systems are obtained syn-, and from (*Z*), the anti-, products.[1] There is substantial impetus for application of the process to carbonyl-stabilized allylic systems,[2] in particular those bearing oxygen at C-4 (Scheme 1), as this would provide synthetically useful, yet otherwise inaccessible, cyclic enones bearing side chains with stereodefined α-hydroxyl groups. Two systems were selected for examination—lithiated (*E*)-4-alkoxy-3-butenoate esters **1** and lithiated γ-crotonolactone **2**. Should reactions of **1** proceed through a 10-membered TS,[1] or of **2** via a 9-membered "exo" TS[3] with a cyclic enone, these will provide enolates **3** and **4** with *equivalent* stereochemistries (Scheme 1). The enolate **3** upon protonation would provide the syn-product **5**. The enolate **4** upon protonation, ring opening, and double-bond isomerization would also give **5**. In both cases, we are unaware of literature precedents.[4]

Scheme 1



Ethyl (*2E*)-4-(benzyloxy)but-2-enoate (**6**)[5] was treated with LDA in THF at −60 °C, then with cyclopentenone, and quenched at the same temperature. However, while reaction took place through C-4, the product was a 60:40 mixture of diastereomers of the (*Z*)-isomer **7** (*cf.* **5**, Scheme 1). The reaction is thus distinct to conjugate



addition of lithiated allylic esters, which react through C-2.[2,6] On the other hand, lithiated butenolide **2** added cleanly to (±)-4-*tert*-butoxycyclopent-2-enone (**8**) in THF at −78 °C to give diastereomers **9**−**12** (60−65% overall), in a ratio of 80:15:3:2, or at −90 °C to give **9** and **10** only (92:8, 83%). The major product **9** corresponds to the syn-isomer (*cf.* Scheme 1),[1,7] and *its formation is in accord with the prediction of Scheme 1.* THF was the best among ether solvents, and HMPA or Lewis acids, such as zinc chloride and magnesium *tert*-butoxide, depressed yields of **9**. The importance of lithium chelation is underscored by the fact that the TMS ether **13** of γ-crotonolactone with Lewis acids in dichloromethane or MeCN at −78 °C with enone **8** gave as major products the *cis*-disubstituted adducts **10** and **12**. Thus, product ratio of **9**−**12** with $SnCl_4$ (0.1 equiv) in dichloromethane was 5:44:3:48 (90%); with HgI_2 in dichloromethane the cis adducts **10** and **12** (50:50) only were formed, albeit in low yield (30%).[8]

Addition of (4*R*)-enone **14**[9] to 2-lithio-1,3-dithiane in THF containing HMPA (2 equiv) at −78 °C gave adduct **15** (86%), treatment of which with TMSOTf (10 mol %) in dichloromethane at room temperature furnished enone **16** (86%).[10] Next, enone **16** at −90 °C was treated with lithiated butenolide **2** in THF to give adducts **17** and **18** (95:5, 52% overall). The structure of the major isomer from racemic enone as revealed by X-ray crystallographic analysis again is in accord with the transition state model of Scheme 1.[22]

Absolute configurations at C-1′ and C-3 in **17** correspond to those at C-4 and C-5 in (+)-brefeldin A **23** (Scheme 2). While the butenolide ring in **17** was opened by LiOH in aqueous MeOH to give the (*E*)-unsaturated acid **19** and the (*Z*)-isomer, the use of LiSPh (1.1 equiv)

† Dedicated to Professor Dr. Dieter Seebach in honor of the occasion of his 60th birthday.

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(1) Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *111*, 5411. Oare, D. H.; Heathcock, C. H. *Top. Stereochem.* **1992** *19* 338.

(2) Haynes, R. K.; Starling, S. M.; Vonwiller, S. C. *J. Org. Chem.* **1995**, *60*, 4690.

(3) However, the stereochemical outcome of the conjugate addition of a five-membered zinc chelate to a cyclopentenone is rationalized in terms of an endo-orientation of reactants: Takahashi, T.; Nakzawa, M.; Kanoh, M.; Yamamoto, K. *Tetrahedron Lett.* **1990**, *31*, 7349.

(4) The proposals were set out in Honours proposal of A.C.R. at the University of Sydney.

(5) Villieras, J.; Rambaud, M.; Graff, M. *Tetrahedron Lett.* **1985**, *26*, 53. Solladié, G.; Hutt, J.; Fréchou, C. *Tetrahedron Lett.* **1987**, *28*, 61.

(6) This result implies that the lithiated ester has the (*Z*)-configuration, in accord with the structure of lithiated allyl ethers; see: Yamamoto, Y.; Yatagi, H.; Maruyama, K. *J. Org. Chem.* **1980**, *45*, 195 and references therein.

(7) Structures of **9**, **10**, and **12** were established by X-ray crystallography at the University of Sydney. Ratios of all isomers were established by measurement of reaction mixtures at 600 MHz

(8) For a related case involving conjugate addition of silyl ketene acetals, see: Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456. Chow, K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 6016.

(9) Eschler, B. M.; Haynes, R. K.; Ironside, M. D.; Kremmydas, S.; Ridley, D. D.; Hambley, T. W. *J. Org. Chem.* **1991**, *56*, 4760.

(10) The use of the catalytic reagent to cleave *tert*-butyl ethers has been described recently: Franck, X.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1995**, *36*, 711.

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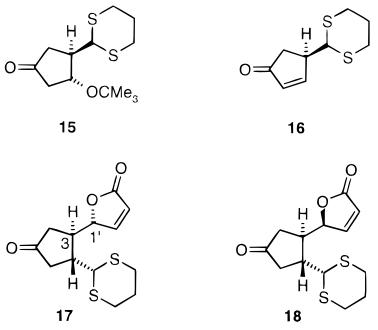
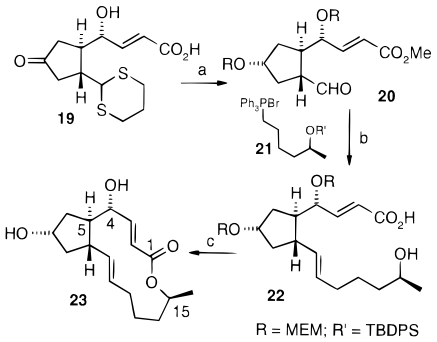


and $TiCl_4$ (1.5 equiv) in THF gave solely the (*E*)-acid (58% overall). This method for opening of butenolides has not been described previously.[11] The acid **19** was esterified, and the free hydroxy group was protected as the MEM ether, a group that, as in a related case,[12] controlled stereoselectivity in the reduction of the cyclopentanone carbonyl with L-Selectride. The resulting alcohol epimers (75:25) were protected as MEM ethers, and the dithiane in the major epimer was converted into the free aldehyde **20** (58%) with an excess of MeI and sodium bicarbonate in aqueous MeCN.[13] The aldehyde with the Wittig reagent from phosphonium salt **21**[14] in THF containing LiBr (1 equiv) gave the alkene (81%, *E*/*Z* 87:13), treatment of which with aqueous HCl in THF and then with LiOH in MeOH gave (*E*)-hydroxy acid **22** (86%).[15] Lactonization and deprotection gave (+)-brefeldin A, mp 203−204 °C; $[\alpha]^{22}_D$ +83.0° (*c* 0.04, MeOH).[16]

Scheme 2[a]



Key: [a](a) (i) CH_2N_2 then MEMCl, *i*-Pr_2NEt , CH_2Cl_2, 12 h (86%); (ii) K-Selectride, THF, −78 °C, 1 h (79%); (iii) MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 10 h (85%); (iv) MeI, $NaHCO_3$, MeCN, rt (58%); (b) (i) *n*-BuLi, phosphonium bromide **21**, LiBr (1 equiv), THF, −78 °C then $KOCMe_3$ (78%, *E*/*Z* 87:13); (ii) 1 mol L HCl, THF, 10 h, rt, workup then LiOH, MeOH, H_2O, 10 h (86%); (c) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 6 h, DMAP, toluene, reflux, 14 h (78%); (ii) $TiCl_4$, CH_2Cl_2, 0 °C, 2 h (96%).

Clearly, the conjugate addition of lithiated butenolide **2** to (*R*)-enone **14** or the (*S*)-enantiomer[9] and to other cyclic enones such as **16** bearing a stereodirecting group at C-4 presents a simple operational means of controlling installation of absolute configuration at oxygen-bearing functional groups exocyclic to the enone. The conjugate addition reactions display a hitherto unrevealed stereoselectivity in the reactions of the intensively examined butenolide.[17]

The facile elimination of *tert*-butoxide from **15** to produce the enantiomerically-equivalent enone **16** is also significant; the enantiomer **14** serves as an operational equivalent of "chiral" cyclopentadienone, which is effective *under aprotic conditions*. The use of racemic 4-acetoxycyclopentenone as an operational equivalent of "racemic" cyclopentadienone was described some years ago,[18] but the enantiomers of the acetoxy enone cannot be easily obtained,[9] and cannot be used under aprotic conditions.

While the current synthesis of brefeldin A is not as convergent as originally planned,[4,19,20] it has clear potential in preparation of analogues.[21,22]

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Supporting Information Available: Experimental procedures for conjugate addition reactions of **2**, lithiated **6**, and **13** with enones, experimental procedures for synthesis of brefeldin A, characterization data for all new compounds, ORTEP plots, and X-ray data for compounds **9**, **10**, **12**, and (*R*,*S*)-**17** (19 pages).

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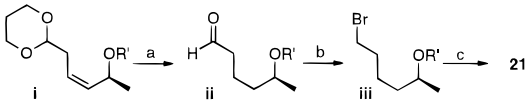
(11) In the original strategy (ref 4), opening of the butenolide with its (*Z*)-configured double bond by alkoxide nucleophiles would be problematical. Conjugate addition of thiolate provides a saturated butanolide whose thiophenoxide-mediated opening is now favorable. Reversible elimination of thiolate provides the more stable (*E*)-unsaturated thioester, which is hydrolyzed on quenching to the acid.

(12) Casy, G.; Gorins, G.; McCague, R.; Olivo, H. F.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1085; Carnell, A. J.; Casy, G.; Gorins, G.; Kompany-Saeid, A.; McCague, R.; Olivo, H. F.; Roberts, S. M.; Willetts, A. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3431.

(13) Smith, A. B.; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 8008.

(14) The phosphonium salt **21** was prepared from the alkene *i* obtained according to a literature sequence for a closely related compound; see: Boon, G. J.; Downham, R.; Kim, K. S.; Ley, S. V.; Woods, M. *Tetrahedron* **1994**, *50*, 7157. (a) Pt/C, H_2, EtOAc, rt (98%) then 70% aqueous HOAc to give **ii** (83%); (b) $NaBH_4$, MeOH at 0 °C (94%) then CBr_4, PPh_3, DMF, 0 °C to give **iii** (95%); (c) PPh_3, MeCN, reflux to give **21** (77%).



(15) Evidently, under these conditions, acid-catalyzed isomerisation of the (*Z*)-alkene takes place.

(16) Corey, E. J.; Wollenberg, R. H. *Tetrahedron Lett.* **1976**, 4705. Corey, E. J.; Wollenberg, R. H.; Williams, D. R. *Tetrahedron Lett* **1977**, 2243: mp 201−202 °C; $[\alpha]^{20}_D$ +90.0 (*c* 0.1, MeOH).

(17) For leading references, see: Boukouvalas, J. In *Encyclopedia of Reagents for Organic Synthesis*; Wiley: Chichester, 1995; Vol. 2, pp 820−823; Vol. 7, pp 5297−5300.

(18) Koeksal, Y.; Raddatz, P.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 472 and references cited therein.

(19) The original intention was to add the vinyl cuprate corresponding to the protected (*S*)-heptenol side chain of brefeldin A to the enone **14** and then, after elimination of butoxide, treat the transposed enone (*cf.* **16**) with the lithiated butenolide **2**. While syntheses of brefeldin A employ conjugate additions of such organocuprates to cyclopentenones, we could not obtain workable yields of adducts. For relevant examples, see refs 4 and 12 and: Bernardes, V.; Kann, N.; Riera, A.; Moyano, A.; Pericas, M. A.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 6670. Kobayashi, Y.; Watatani, K.; Kikori, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 6125.

(20) For recent syntheses see refs 12 and 19 and: Miyaoka, H.; Kajiwara, M. *J. Chem. Soc., Chem. Commun.* **1994**, 483. Tomioka, K.; Ishikawa, K.; Nakai, T. *Synlett* **1995**, 901. Kim, D.; Lim, J. I. *Tetrahedron Lett.* **1995**, *36*, 5035.

(21) For application of brefeldin A derivatives in induction of cell differentiation and apoptosis in cancer cell lines, see: Zhu, J.-W.; Hori, H.; Nojiri, H.; Tsukuda, T.; Taira, Z. *Bioorganic Med. Chem. Lett.* **1997**, *7*, 139.

(22) The authors have deposited atomic coordinates for **9**, **10**, **12**, and *(R,S)*-**17** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.