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A New Approach to (+)-Brefeldin A *via* a Nickel-catalyzed Coupling Reaction of Cyclopentenyl Acetate and Lithium 2-Furylborate

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Abstract: Coupling reaction of 2 with 2-furylborate 14 in the presence of the nickel catalyst afforded 1,4-isomer 5 regio- and stereoselectively and the product 5 was applied to the synthesis of Bartlett's brefeldin intermediate 11. Copyright © 1996 Elsevier Science Ltd

Transition metal-catalyzed coupling reactions of cyclopentadiene monoepoxide (1) or its synthetic equivalent such as 2 with "hard" organometallic reagents, especially those possessing metal- sp^2 -carbon bond is an attractive processes for the synthesis of biologically important cyclopentanoids such as hitachimycin, hybridalactone, brefeldins, multifiden *etc.* (eq. 1). Among the organometallic/metal-catalyst systems published so far for coupling with acyclic allylic derivatives,¹ organotin/Pd is the only one which has been applied to cyclopentenyl derivatives.² Although perfect stereocontrol is obtained in the reaction of 1 with all three organotins examined, the observed low regioselectivity suggests difficulty of regiocontrolled installation of "hard" species onto the 5-membered ring system.³



Recently we have reported regio- and stereoselective coupling reactions of secondary allylic carbonates and lithium organoborates in the presence of nickel catalysts (eq. 2).⁴ We expected that due to the small radius of nickel, the nickel atom on intermediate **3** is closely bound to the π -allyl moiety and, consequently, that transmetallation and subsequent reductive elimination processes would become more susceptible to a small steric hindrance and/or an electronic effect, thus producing the 1,4-isomer regioselectively. We selected brefeldin A (4)⁵ as the target molecule and examined such an effect in the asymmetric synthesis of the new intermediate **5** where the furyl group is chosen for the C₁-C₄ (brefeldin A numbering) moiety of **4**. Since furans are stable

$$R^{1} \xrightarrow{R^{2}} R^{2} \xrightarrow{R^{3} - B(OMe)_{3}Li}_{OCOOEt} R^{1} \xrightarrow{R^{1}} R^{2} \xrightarrow{R^{3}} R^{3}$$

$$R^{1} = Ph, COOEt \qquad R^{3} = Ph, 2 \cdot Furyl,$$
Alkenyl



under basic, weakly acidic, and mild oxidative conditions, a number of reactions are operative for installation of the C_{10} - C_{16} side chain and functional group transformations. Herein we report the regio- and stereoselective formation of optically active 5 and its conversion to Bartlett's intermediate 11^{5c} (Scheme 1).

Although epoxide 1⁶ and acetate 2⁷ are readily available as optically active compounds, preliminary experiments were carried out with racemic substrates $(rac-1, rac-2)^8$ and 3 equiv of lithium 2-furylborate 14 (Fu = 2-furyl) in the presence of 5-10 mol% of the nickel catalyst (NiCl₂(dppf) or NiCl₂(PPh₃)₂) under the conditions reported (THF, 50-60 °C, 4-12 h).^{4a} When the epoxide *rac*-1 was submitted to the reaction with NiCl₂(PPh₃)₂, all four possible isomers *rac*-5,15-17^{9,10} were produced in a ratio of 42 : 33 : 23 : 2 (determined by 300 MHz ¹H NMR) and in low yield (<30%) (eq. 3). No other conditions (NiCl₂(dppf), room temp., or Et₂O) improved the selectivity and yield. On the other hand, the acetate *rac*-2 did afford the *trans* isomers, *rac*-5 and -15, in a ratio of 88 : 12 and in 78% yield with NiCl₂(PPh₃)₂ (eq. 4). A similar ratio (83 : 17) was observed with NiCl₂(dppf) (55% combined yield). In the ¹H NMR spectra of the crude products, no *cis* isomer(s) were detected. It should be noted that this is the first example to realize practically high levels of regioselection in the coupling of "hard" organometallics and π -allyl metals derived from cyclopentenyl compounds.¹¹ The coupling reaction was carried out again with optically active 2^{7a} ([α]²⁸_D = -66 (*c* 0.82, CHCl₃); for 2 of >96% ee, ^{7a} [α]²⁰_D = -68 (CHCl₃)) and borate 14 to afford 5 ([α]²⁹_D = +190 (*c* 0.46, CHCl₃)) and 15 ([α]²⁹_D = -148 (*c* 0.15, CHCl₃)), which were separated easily by silica gel column chromatography.



The optically active side chain 12 ($[\alpha]^{20}_D = +14$ (c 0.99, Et₂O); the calculated value for the pure enantiomer,^{5d} $[\alpha]^{20}_D = +12.6$ (c 1.04, Et₂O)) was prepared from (R)-(-)-epichlorohydrin (18) (98.8% ee) by the route shown below. Hydrozirconation of acetylene 20 was conveniently carried out by the method of Lipshutz.¹²





Scheme 1. (a) PCC, CH₂Cl₂; (b) 13 (12, *n*-BuLi then LiCu(CN)Th), -78 °C, THF; (c) LiB(*s*-Bu)₃H, THF, -78 °C; (d) HCOOH, DEAD, PPh₃ then NaOH; (e) MOMCl, *i*-Pr₂NEt; (f) Bu₄NF. THF; (g) NBS, C₅H₅N, acetone/H₂O, -20 °C, 30 min then rt., 4 h; (h) NaClO₂, resorcinol, *t*-BuOH, buffer (pH 3.6).

Oxidation of 5 with PCC proceeded without affecting the furan ring^{13a} to afford cyclopentenone 6 $([\alpha]^{30}_{D} = +280 \ (c \ 0.08, CHCl_3))$ in 71% yield (Scheme 1). 1,4-Addition of the higher order cuprate 13 (1.5 equiv) derived from 12 [(1) *n*-BuLi, -70 °C, 1 h; (2) LiCu(CN)(2-Th),¹⁴ -70 °C] provided cyclopentanone 7 quantitatively. Reduction of 7 using LiB(s-Bu)₃H followed by Mitsunobu inversion furnished 8 and the C₇ epimer in a ratio of 3 : 1. Protection (MOMCl, *i*-Pr₂NEt) followed by desilylation (Bu₄NF) gave alcohol 9 in 83% yield.

Conversion of the furan ring of 9 into the 4-oxo-2-butenoic acid moiety was then explored. Although attempts to apply the literature protocols (PCC/CH₂Cl₂, ^{13a,b} Br₂/aq. acetone^{13c} or aq. MeCN^{13d}) were all in vain in our hand, NBS in aq. acetone was found to be quite effective, furnishing the aldehyde 10 in 71% yield.¹⁵ Further oxidation of 10 with NaClO₂ in the presence of resorcinol¹⁶ provided the acid 11 in 78% yield, whose ¹H NMR spectrum was in good agreement with that reported by Bartlett.^{5c}

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- 8. When racemic compounds are used, prefix "rac-" is added to the numbers to differentiate them with the optically active compounds.
- Relative stereochemistry of the C₅ carbon of 1,4-isomers *rac-5* and -16 was determined based on the fact that *cis* vic coupling constant is larger (7-9 Hz) than *trans* one (3-5 Hz).^{10a-c} Stereochemistry of 1,2-isomers were assigned by analogy with 1,4-isomers.
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