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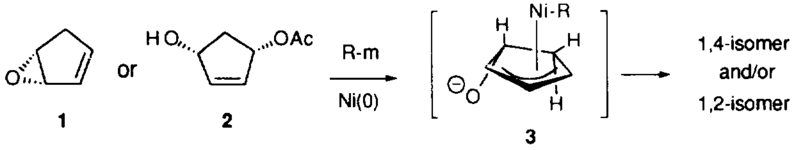
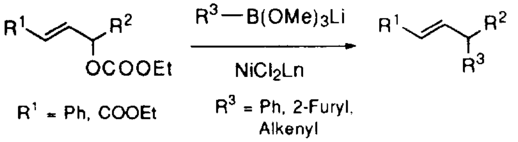
Abstract: *Coupling reaction of **2** with 2-furylborate **14** in the presence of the nickel catalyst afforded 1,4-isomer **5** regio- and stereoselectively and the product **5** was applied to the synthesis of Bartlett's brefeldin intermediate **11**.* Copyright © 1996 Elsevier Science Ltd

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]

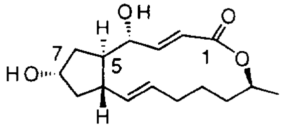


(1)

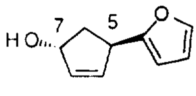
Recently we have reported regio- and stereoselective coupling reactions of secondary allylic carbonates and lithium organoborates in the presence of nickel catalysts (eq. 2).[4] We expected that due to the small radius of nickel, the nickel atom on intermediate **3** is closely bound to the π-allyl moiety 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 C_1-C_4 (brefeldin A numbering) moiety of **4**. Since furans are stable



(2)



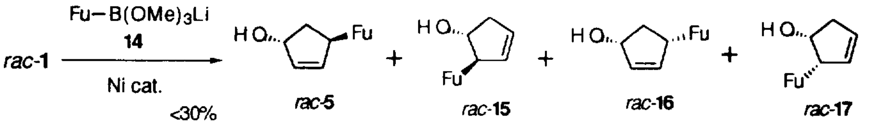
Brefeldin A (**4**)



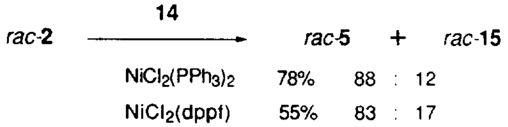
5

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 **1**[6] and acetate **2**[7] 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 ($NiCl_2$(dppf) or $NiCl_2(PPh_3)_2$) under the conditions reported (THF, 50-60 °C, 4-12 h).[4a] When the epoxide *rac*-**1** was submitted to the reaction with $NiCl_2(PPh_3)_2$, all four possible isomers *rac*-**5**,**15**-**17**[9,10] were produced in a ratio of 42 : 33 : 23 : 2 (determined by 300 MHz ^{1}H NMR) and in low yield (<30%) (eq. 3). No other conditions ($NiCl_2$(dppf), room temp., or Et_2O) 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 $NiCl_2(PPh_3)_2$ (eq. 4). A similar ratio (83 : 17) was observed with $NiCl_2$(dppf) (55% combined yield). In the ^{1}H 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] ($[\alpha]^{28}_D$ = -66 (*c* 0.82, $CHCl_3$); for **2** of >96% ee,[7a] $[\alpha]^{20}_D$ = -68 ($CHCl_3$)) and borate **14** to afford **5** ($[\alpha]^{29}_D$ = +190 (*c* 0.46, $CHCl_3$)) and **15** ($[\alpha]^{29}_D$ = -148 (*c* 0.15, $CHCl_3$)), which were separated easily by silica gel column chromatography.

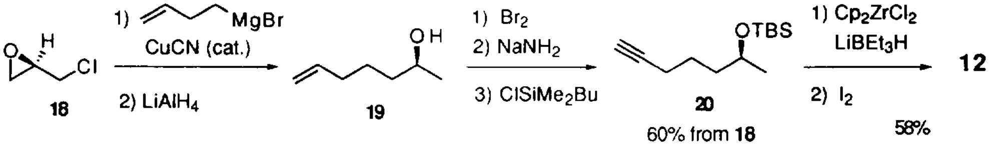


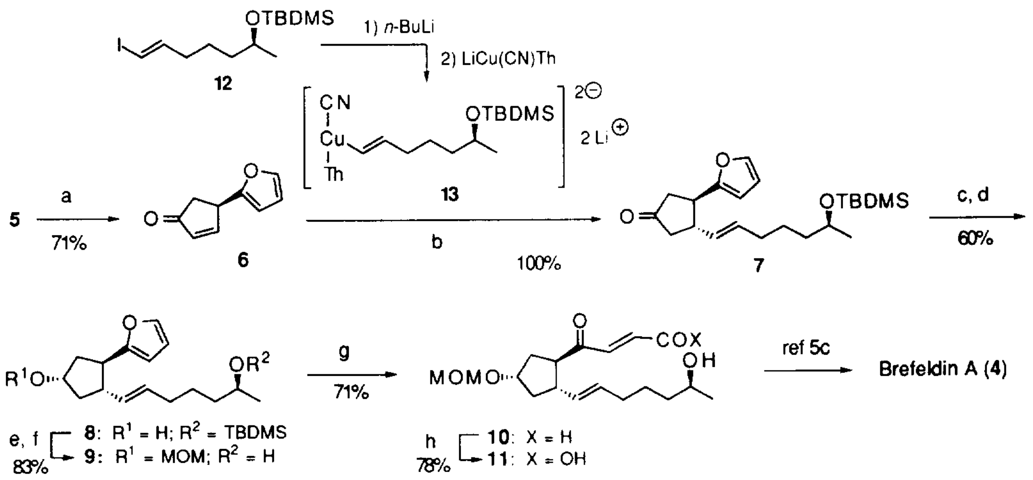
(3)



(4)

The optically active side chain **12** ($[\alpha]^{20}_D$ = +14 (*c* 0.99, Et_2O); the calculated value for the pure enantiomer,[5d] $[\alpha]^{20}_D$ = +12.6 (*c* 1.04, Et_2O)) 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, CH_2Cl_2; (b) **13** (**12**, *n*-BuLi then LiCu(CN)Th), -78 °C, THF; (c) LiB(*s*-Bu)$_3$H, THF, -78 °C; (d) HCOOH, DEAD, PPh_3 then NaOH; (e) MOMCl, *i*-Pr_2NEt; (f) Bu_4NF, THF; (g) NBS, C_5H_5N, acetone/H_2O, -20 °C, 30 min then rt., 4 h; (h) $NaClO_2$, 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)$_3$H followed by Mitsunobu inversion furnished **8** and the C_7 epimer in a ratio of 3 : 1. Protection (MOMCl, *i*-Pr_2NEt) followed by desilylation (Bu_4NF) 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/CH_2Cl_2,^{13a,b} Br_2/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 $NaClO_2$ in the presence of resorcinol^{16} 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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