Pergamon

Tetrahedron Letters, Vol. 38, No. 10, pp. 1693-1696, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00192-5

An Efficient Formal Synthesis of Balanol via the Asymmetric Epoxide Ring Opening Reaction[1]

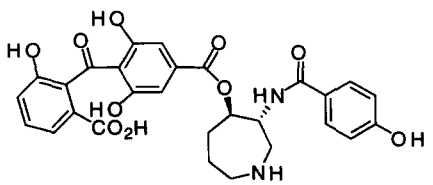
Michael H. Wu and Eric N. Jacobsen*

Department of Chemistry and Chemical Biology, Harvard University

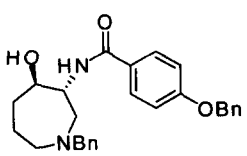
Cambridge, Massachusetts 02138

Abstract: An efficient formal synthesis of balanol is described. The thirteen-step sequence features a highly enantioselective (92% ee) ring opening of 1,4-cyclohexadiene monoepoxide with $TMSN_3$ catalyzed by the Cr-salen complex **3**. A selective Beckmann rearrangement followed by amide reduction and nitrogen functionalization affords **2**, thus completing a formal synthesis of balanol in 31% overall yield.

The protein kinase C (PKC) family of serine/threonine-specific protein kinases serves a crucial role in cellular growth control, regulation, and differentiation.[2] The deleterious effects of unregulated PKC activation, which include carcinogenesis, inflammation, and cardiovascular disorders,[3] have given rise to focused interest in the development of inhibitors of this class of enzymes. One of these, balanol (**1**), is a metabolite produced by the fungus *Verticillium balanoides* which has been shown to inhibit PKC at low nanomolar concentrations.[4] As part of our efforts to develop practical and enantioselective methods for the synthesis of biologically important compounds,[5] we have investigated the application of the asymmetric ring opening (ARO) methodology recently developed in our laboratory to the synthesis of balanol.[6]

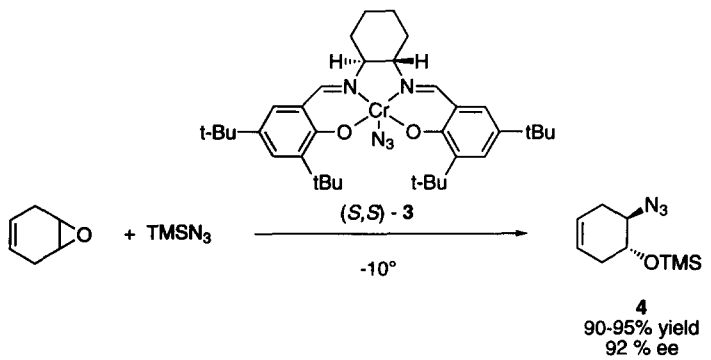


1



2

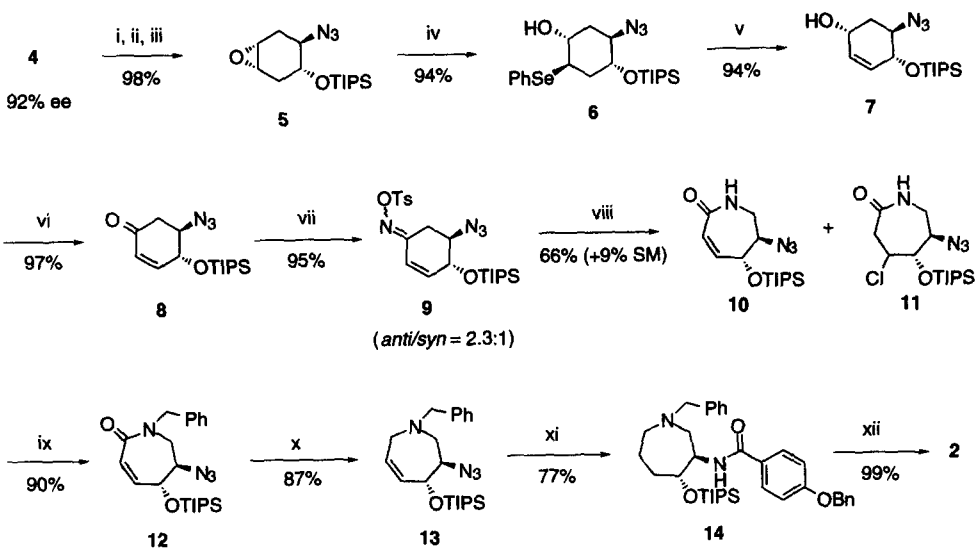
The ring-opening of 1,4-cyclohexadiene monoepoxide carried out under previously reported conditions (room temperature, 2 mol% catalyst, 3.0 M epoxide in Et_2O)[5] required 46 hours to reach completion and provided the azido silyl ether product **4** with only modest enantioselectivity (81-83% ee). The slow reaction rate attained under these conditions limited the possibility of performing the reaction at lower temperatures to enhance enantioselectivity. However, the fact that the ARO displays a second-order dependence on catalyst concentration[7] suggested that a significant rate enhancement might be gained upon increasing the catalyst concentration. Indeed, under solvent-free conditions and a higher catalyst loading (7.5 mol %, [**3**] ≈ 0.3 M), complete epoxide conversion occurred within 24 h at -10 °C to afford the azido silyl ether in 92% enantiomeric excess. Simple distillation of the product and recycling of the catalyst allowed the convenient production of 15 grams (71 mmol) of **4** in 90-95% overall yield using 0.32 g (0.50 mmol) of **3**.



4
90-95% yield
92 % ee

With enantiomerically-enriched **4** in hand, the regioselective oxidation of the alkene was addressed (Scheme 1). Deprotection of **4**, followed by a molybdenum-catalyzed directed epoxidation[8] of the azido alcohol afforded the corresponding epoxy alcohol in 98% yield as a single diastereomer (^{1}H NMR analysis). Epoxide ring opening of the TIPS ether **5** with sodium phenyl selenate afforded **6** as a single product.[9] An oxidation and elimination sequence then led to allylic alcohol **7** (94%), which was subjected to catalytic oxidation using NaOCl in the presence of TEMPO[10] to the α,β-unsaturated ketone **8** (97% yield).[11] Preparation of the oxime tosylate esters afforded a 2.3:1 mixture of isomers in 95% overall yield.[12]

Scheme 1



Reagents and conditions: i) cat. TFA, MeOH, rt; ii) $Mo(CO)_6$, TBHP, PhH, reflux; iii) TIPSCl, KH, THF, 0°; iv) PhSeSePh, $NaBH_4$, EtOH; v) H_2O_2, $NaHCO_3$, THF; then iPr_2NH, PhH, reflux; vi) TEMPO, NaOCl, CH_2Cl_2 vii) $H_2NOH{\cdot}HCl$, pyridine, CH_2Cl_2; then TsCl, Et_3N, CH_2Cl_2; viii) excess $TiCl_3(OiPr)$, CH_2Cl_2, rt; ix) KH, BnBr, THF; x) AlH_3, THF, 0°; xi) H_2, PtO_2, EtOAc; then ArCOCl, Et_3N, CH_2Cl_2, 0° to rt; xii) TBAF, THF, rt.

The selective ring expansion of oxime mixture **9** was investigated next. While there is ample precedence for the selective migration of mixtures of *syn* and *anti* α,β-unsaturated oximes, harsh acidic conditions are typically required to effect the rearrangement.[13] After screening several Lewis acids, we found that $TiCl_3$(O-iPr) was especially effective in promoting the conversion of the *syn/anti* oxime mixture to the desired amide **10** in moderate yield, with the saturated amide **11** obtained as a by-product of the reaction. The mixture of amides **10/11** was then cleanly converted (90%) to the *N*-benzyl derivative **12**, with *in situ* elimination of the undesired β-halogen substituent in **11**. Reduction of the lactam with AlH_3 afforded azepene **13** (87%), where surprisingly the azide was not affected under the reaction conditions. Hydrogenolysis of the azide followed by acylation of the amine afforded the hexahydroazepine derivative **2** (77%, 2 steps) with spectral characteristics in full agreement with the published data.[6b]

The Cr-mediated ARO thus allows the construction of both stereogenic centers of balanol in a single catalytic step. Regioselective oxidation and ring expansion processes led to an efficient synthesis of the protected balanol core in twelve steps and 31% overall yield from **4**. In addition, five, six, and seven-membered ring analogs of the core are accessible in high enantiomeric excess using the ARO

methodology, which could allow the generation of structurally diverse compounds through solid-phase combinatorial synthesis for biological evaluation as potential PKC inhibitors.[14]

Acknowledgment. This research was supported by the NIH (GM-43214). We thank Professors J. Aubé and G.C. Fu for helpful discussions.

References and Notes

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(*Received in USA* 3 *January* 1997; *accepted* 20 *January* 1997)