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An Enantioselective Strategy to Macrocyclic Bisindolylmaleimides. An Efficient Formal Synthesis of LY 333531

Barry M. Trost* and Weiping Tang

Department of Chemistry, Stanford University, Stanford, California 94305-5080

bmtrost@leland.stanford.edu

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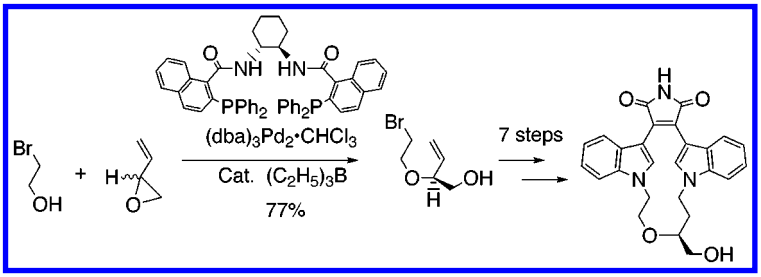
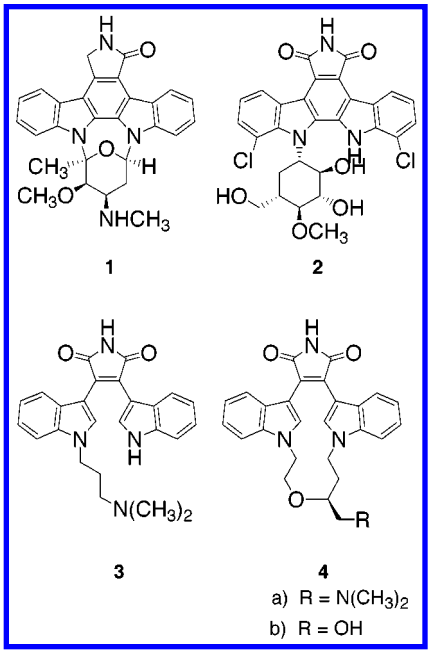
ABSTRACT



The ability to employ a bromo alcohol as a nucleophile in a palladium-catalyzed dynamic kinetic asymmetric transformation leads to an efficient synthesis of a selective PKC inhibitor under clinical development.

Protein kinase C (PKC), a family of at least 11 isomers of serine/threonine specific kinases, has become an important target for development of new therapies.[1] Selective inhibition of overactive PKC isozymes may offer a unique therapeutic approach. The discovery of staurosporine (**1**)[2] and related compounds such as rebeccamycin (**2**)[3] as PKC inhibitors stimulated activities to design selective inhibitors of one or more isozymes in order to create useful drugs. The bisindolylmaleimide **3** proved to be a PKC kinase selective agent.[4]

Conformationally restricted analogues represent an attractive structural type to create more effective agents.[5] The Lilly group embarked on a novel approach to impart conformational restrictions via formation of macrocycles and designed



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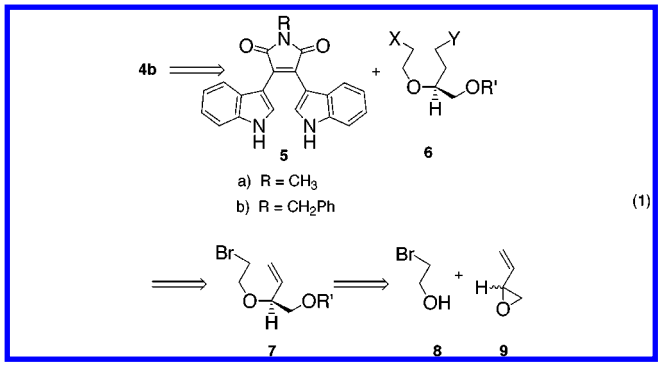
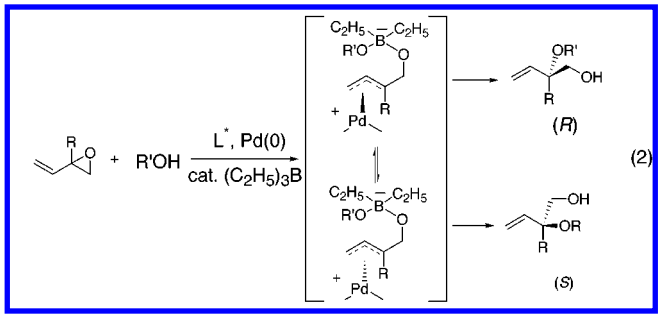
LY 333531 (**4a**).[6] This compound selectively inhibits PKCβ, and PKCβ2 over PKCα and is several orders of magnitude more selective for PKCβ isozymes in comparison to other ATP-dependent kinases. Lilly is developing this compound for the treatment of retinopathy associated with diabetic complications.



(1)

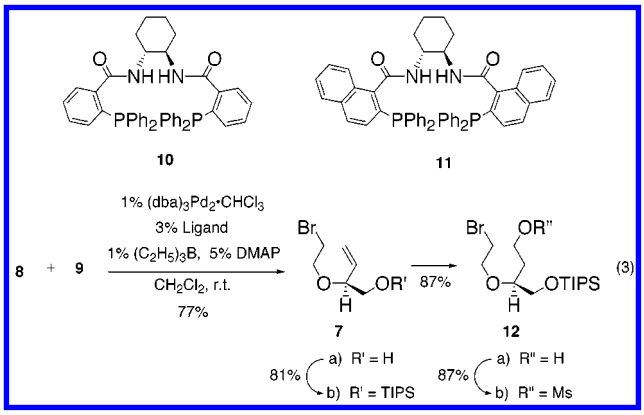
The retrosynthetic analysis recognizes its availability from the alcohol **4b**, which in turn should derive from a macrocyclization of a core bisindolylmaleimide **5** and a bisalkylating agent **6** (eq 1).[7] The efficiency of this strategy depends on the availability of the chiral bisalkylating agent. A number of routes were investigated starting from scalemic building blocks such as dimethyl (*S*)-maleate, (*R*)-glycidol, and (*R*)-chloro-2,3-propanediol.[7] We envisioned an alternative strategy based upon a dynamic kinetic asymmetric transformation (DYKAT) of the simple racemic building block Epb (epoxybutadiene) under commercial development by Eastman Chemical Company.[8] This strategy derives from the ability of a π-allylpalladium complex to undergo facile migration from one face to the other via $\pi-\sigma-\pi$ equilibration as well as to utilize coordination to boron to direct regioselectivity as depicted in eq 2. The synthesis of LY



(2)

333531 requires an alcohol such as 2-bromoethanol wherein an interesting chemoselectivity issue arises—intramolecular O-alkylation to form ethylene oxide versus intermolecular alkylation to form bromoether **7**.

Commercially available 2-bromoethanol and butadiene monoepoxide reacted smoothly in the presence of a Pd(0) complex bearing our standard ligand **10**[9] to give the desired bromoether in good yield but only 58% ee (eq 3). The enantioselectivity is consistent with our earlier results using ligand **10** to peform a DYKAT with Epb **9**. As anticipated, switching to our naphthyl ligand **11** increased the ee to 92%.[10] Performing the reaction with only 1 equiv of bromoethanol led to a small amount of a double alkylation product wherein the primary alcohol **7a** underwent addition of a second molecule of Epb. Using an excess of 2-bromoethanol eliminated this byproduct so that **7a** was isolated in 77% yield.



(3)

Formation of this bisalkylating agent anticipated the ultimate need to differentiate between two primary hydroxyl groups. Thus, the primary alcohol of **7a** was first silylated to form **7b** (eq 3) using TIPS-OSO_2CF_3 [$(C_2H_5)_3N$, CH_2Cl_2, 0 °C]. Again, no complications from cyclization to form a 1,4-dioxane occurred. Hydroboration with 9-BBN-H followed by oxidation with hydrogen peroxide using sodium acetate as base provided the alcohol **12a** uneventfully. Finally, mesylation under standard conditions gave the bisalkylating agent (**12b**) in four steps and 46% overall yield.

To demonstrate the viability of this bisalkylating agent for the synthesis of LY 333531, the macrocycle was formed following the Lilly protocol as shown in eq 4. The Lilly group has reported yields ranging from 48% to 68% with typical slow addition times of 60 h.[7] With bisalkylating agent **12b** and the *N*-benzyl-bisindolylmaleimide **5b**, a 77% yield was realized using an 8 h addition time at the same final concentration of the Lilly group (0.029 M). To complete the formal synthesis, the macrocycle **13** was converted to **4b**. Following the Lilly protocol, base hydrolysis followed by acidic workup gave a mixture of the anhydride **14a** and its desilylated analogue **14b**, which was taken directly on. Imide formation with HMDS in methanolic DMF followed by TBAF to complete the remaining desilylation produced the

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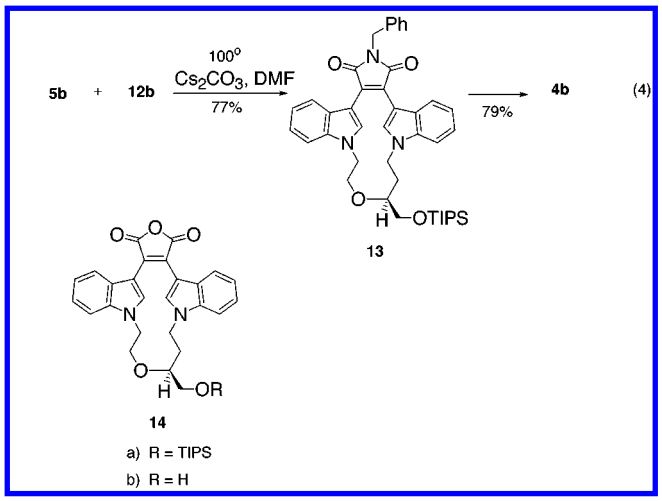
Lilly intermediate **4b** in 79% yield from *N*-benzyl imide **13**. The observed rotation $[\alpha]_D = -10.41$ (*c* 0.28, CH_3OH) is in excellent agreement with the one reported.[7]



The Pd-catalyzed DYKAT of racemic vinyl epoxides serves as a useful strategy for constructing valuable chiral building blocks. The ability to employ bromo-substituted alkyl alcohols in such alkylations without complications demonstrates the exquisite chemoselectivity the reaction possesses. A simplified procedure for the synthesis of a bisalkylating agent useful in the synthesis of LY 333531 demonstrates the utility. Starting from two inexpensive commercially available reactants, racemic Epb and 2-bromoethanol plus the bisindolylmaleimide **5b**, alcohol **4b**, the penultimate precursor, was available in eight steps and 28% overall yield. Furthermore, the sequence has not been optimized. For example, the conversion of **13** to **4b** involved a three-step sequence, although no intermediates need be isolated. Nevertheless, a one-pot hydrogenolysis−desilylation may be envisioned. In summary, combining the commercial development of Epb with the palladium-catalyzed DYKAT provides a beneficial strategy for the synthesis of chiral synthons.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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