A Catalytic Enantioselective Approach to Chromans and Chromanols. A Total Synthesis of (−)-Calanolides A and B and the Vitamin E Nucleus

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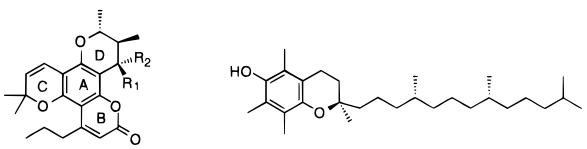
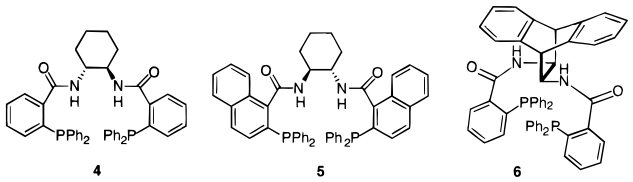
Interest in calanolide A and B, isolated from several tropical plants of the genus *Calophyllum* by Polonsky over 40 years ago,[1] remained dormant until the mid-nineties. A flurry of synthetic interest[2] was spawned by the discovery that these coumarins were HIV-1-specific reverse transcriptase inhibitors, with calanolide A and B being the most potent.[3] They are of special interest because they are active against AZT-resistant strains of HIV-1. Despite a number of synthetic efforts, only one asymmetric synthesis of calanolides has been reported, and it required a stoichiometric asymmetric reagent to create the chirality.[2d]

The key structural feature, both synthetically and biologically, of the calanolides is the trisubstituted chroman ring.[4] Its stereochemistry, both relative and absolute, is the major challenge in the synthesis of this biologically important class of molecules. Furthermore, chiral chromans are prevalent in other natural products, such as vitamin E, **3**.[5] We therefore sought a general



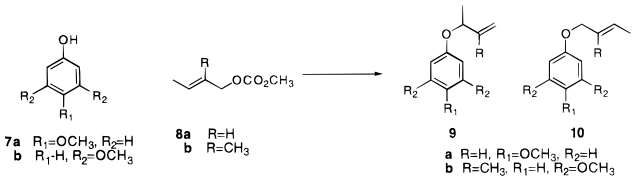
route to the enantioselective preparation of chromans in which the chirality was introduced in a catalytic reaction. We envisioned an asymmetric O-alkylation of phenols followed by aromatic substitution to close the ring.[6] Besides the chromanol stereochemistry, the synthesis of calanolides requires an efficient method for the regioselective annulation of three rings onto a phloroglucinol core, the chromanol (ring D), a chromene (ring C), and a coumarin (ring B). Herein, we describe a new paradigm for the enantioselective synthesis of chromans and chromanols which culminates in a total synthesis of calanolides A and B and the chroman nucleus of vitamin E.

An asymmetric synthesis of chromans requires that the palladium-catalyzed allylic alkylation of phenols must be both enantio- and regioselective.[7] For example, our approach to the preparation of the calanolide ring D chromanol requires a palladium-catalyzed alkylation with tiglyl methyl carbonate wherein attack of the phenol occurs at the more substituted terminus of the π-allyl unit. However, previous work has shown that phenols, especially ortho-substituted phenols, show a propensity for attack at the primary carbon of unsymmetrical π-allylpalladium complexes.[8] Therefore, our modular ligands (**4**−**6**)[9] must not only provide a mechanism for enantioselectivity but



must also be able to *reverse the intrinsic regioselectivity* for attack of phenols on these intermediates.[10]

We tested the feasibility to exercise regio- as well as enantiocontrol by examining the palladium-catalyzed allylic alkylation of 4-methoxyphenol **7a** with crotyl methyl carbonate **8a** (see Table



1 in Supporting Information). We were delighted to find that using 3% ligand **4** with 1% Pd_2dba_3·$CHCl_3$ afforded the secondary aryl ether **9a**[11] with excellent regioselectivity and 60−68% ee. Lowering the temperature improved the enantioselectivity, but as we have previously observed,[7,12] there was an optimal temperature below which the enantioselectivity deteriorates. There was a clear influence of concentration on both the regio- and enantioselectivity of the reaction. Slowing the rate of the nucleophilic addition step by lowering the palladium catalyst loading to 0.1% and the concentration of the reaction to 0.1 M enabled us to isolate the secondary aryl ether **9a** in a 94:6 ratio and 83% ee. With this result in hand, we examined the palladium-catalyzed reaction using tiglyl methyl carbonate **8b**, the substrate required for the calanolide synthesis. The palladium-catalyzed reaction with 3,5-dimethoxyphenol **7b** and the tiglyl carbonate in the presence of ligand **4** afforded the secondary ether **9b** in 90% ee but in slightly diminished regioselectivity (84:16). Changing to the anthracene-based ligand **6** in THF improved the

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(4) For syntheses of ring D, see: Rama Rao, A. V.; Gaitonde, A. S.; Prakash, K. R. C.; Prahlada Rao, S. A. *Tetrahedron Lett.* **1994**, *35*, 6347. Ishikawa, T.; Oku, Y.; Ken-Ichiro, K.; Ishii, H. *J. Org. Chem.* **1996**, *61*, 6484.

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(6) This approach is conceptually different from other chroman syntheses in which the C−C bond is formed first, followed by C−O bond formation. For a recent enantioselective example of this, see: Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063.

(7) We have previously reported on the use of **8a** and **8b** as substrates for enantioselective allylations of sodium benzenesulfinate, a nucleophile which shows a propensity for secondary attack even in the presence of achiral ligands. Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6257.

(8) (a) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. (b) Goux, C.; Lhoste, P.; Sinou, D. *Synlett* **1992**, 725. (c) Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585.

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(10) An alternative approach to the control of regioselectivity utilizes aryl allyl carbonates as substrates; however, poor enantioselectivty (11%) was obtained. Consiglio, G.; Scalone, M.; Franco, R. *J. Mol. Catal.* **1989**, *50*, L11.

(11) The absolute stereochemistry was determined by hydrogenating **9a** and comparing the saturated product to an authentic sample prepared by Mitsonobu reaction of **7a** with (*R*)-2-butanol.

(12) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.

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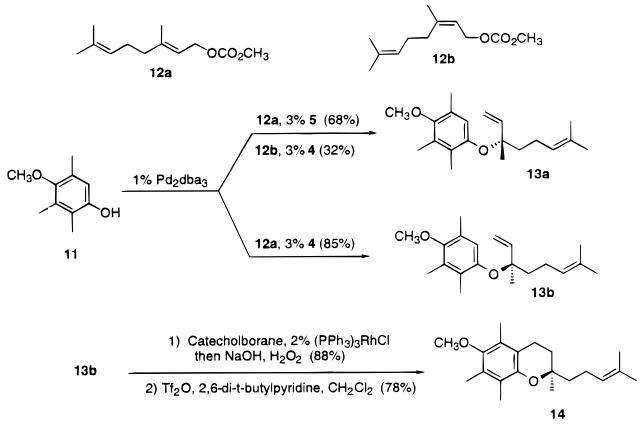
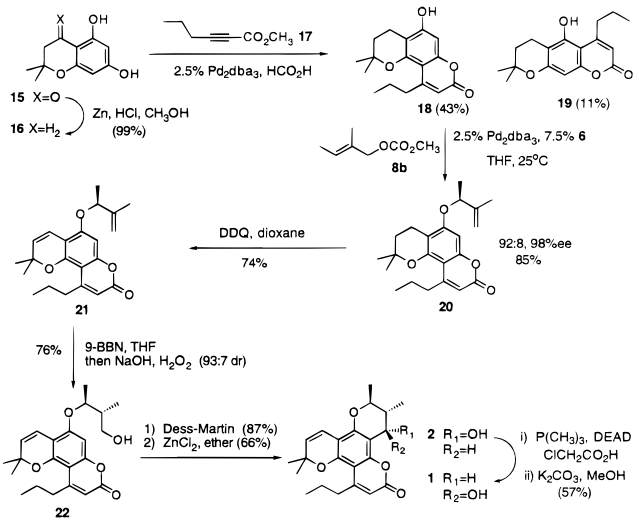
regioselectivity to 91:9 without much deterioration of the enantiomeric excess.

With the technology to prepare secondary aryl ethers in hand, we tackled the much more difficult problem of constructing chiral tertiary ethers from geranyl methyl carbonate **12a**. This substrate



had previously been shown to afford the primary ether as the sole product in phenol allylations with achiral phosphine ligands.[8b] We were pleased to find that the regioselectivity of the palladium-catalyzed reaction of the phenol **11** with **12a** was reversed in the presence of ligand **4**, affording the tertiary ether **13b**[13] in excellent regioselectivity (92:8) and 76% ee. It is important to note that when neryl methyl carbonate **12b** was employed as substrate, using ligand **4**, the enantiomeric ether **13a** was obtained in 91:9 regioselectivity and 76% ee. This implied that the catalyst recognized the same enantiotopic face of the olefin, but since the olefin and, consequently, π-allyl geometries are different, nucleophilic attack gave rise to mirror image products (**13a** and **13b**).[14] Therefore, the stereochemistry of the olefin is conserved during the allylic alkylation reaction. Tightening the chiral pocket with the naphtho-linked ligand **5** improved the regioselectivity to an excellent 98:2 giving **13a** of 77% ee. The completion of the synthesis of the chiral chroman required cyclization, preferably by electrophilic aromatic substitution. To this end, **13b**, obtained from the geranyl substrate using ligand **4**, was chemoselectively hydroborated with catecholborane in the presence of 2% Wilkinson's catalyst.[14] Upon activation of the primary alcohol as its triflate, the latter spontaneously underwent electrophilic cycloalkylation to the chroman **14**, the core of the tocopheryls.

Our synthesis of the calanolides began with Clemmensen reduction[16] of ketone **15**, readily available from phloroglucinol in one step.[17] The phenol **16** was coupled with alkyne **17** under our recently developed palladium-catalyzed coumarin-formation reaction.[18] Under our conditions, complete chemoselectivity for the less sterically hindered hydroxyl group was achieved; however, a 4:1 mixture of regioisomeric coumarins **18** and **19** was obtained. We were pleased to find that even with the sterically demanding phenol **18** as a nucleophile, palladium-catalyzed allylic alkylation with tiglyl methyl carbonate **8b** afforded the secondary ether in excellent regio- (92:8) and enantioselectivity (98% ee). This reaction exemplifies the ability of this class of ligands to overwhelm the inherent selectivity of bulky phenol allylation. Model studies indicated that introduction of the ring C unsatura-



tion after construction of the ring D chromanol was problematic. We therefore oxidized ring C to the chromene **21**, using DDQ, at this earlier stage. Chromene **21** was chemoselectively hydroborated with 9-BBN to afford the alcohol **22** with 93:7 diastereomeric ratio for the newly formed stereocenter.[19] The alcohol was then readily oxidized with the Dess−Martin periodinane, and the resulting aldehyde diastereoselectively cyclized with $ZnCl_2$ to afford the thermodynamically less stable ent-calanolide B(**2**) (10:1 diastereoselectivity). Conversion of ent-calanolide B(**2**) to ent-calanolide A(**1**) is accomplished by a Mitsunobu inversion.[2d] The synthesis of the natural enantiomers simply requires the use of the mirror image ligand of **6**.

This strategy of asymmetric regioselective O-alkylation followed by electrophilic aromatic substitution to form the C−C bond constitutes an effective approach for enantioselective chroman and chromanol synthesis. It is feasible because the chiral pocket of the ligand, rather than the substrate, dictates both the regio- and enantioselectively of the initial O-alkylation.[20] To a first approximation, the ability to exercise regiocontrol may be understood by the steric issues associated with the alkene−palladium complex initially formed in the alkylation.[21] Coordination to a less substituted double bond is favored both electronically and sterically which then directs the nucleophile to the more substituted allyl terminus. The large steric demands of the catalyst pocket appear to make this factor dominant in the product-controlling step of the reaction. It now appears that this family of catalysts may control selectivities beyond enantioselectivity, which greatly expands their utility in synthesis. However, the complexity of the events associated with these alkylations make such simple explanations tenuous. Efforts to fully understand these selectivity issues are ongoing.

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Supporting Information Available: Experimental procedures and characterization data for **1**, **2**, **9a**,**b**, **13a**,**b**, **14**, **16**, and **18**−**22** and Table 1 (10 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(14) Absolute configuration determined by comparison with rotation of **13b** reported in ref 13b.

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(19) Clark, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

(20) For recent papers on controlling the regioselectivity of Pd-catalyzed allylic alkylations, see: Pretot, R.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 323. Hayashi, T.; Kawatsura, H.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681.

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