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A LOW-TEMPERATURE MITSUNOBU REACTION FOR THE INVERSION OF STERICALLY HINDERED SECONDARY ALCOHOLS.

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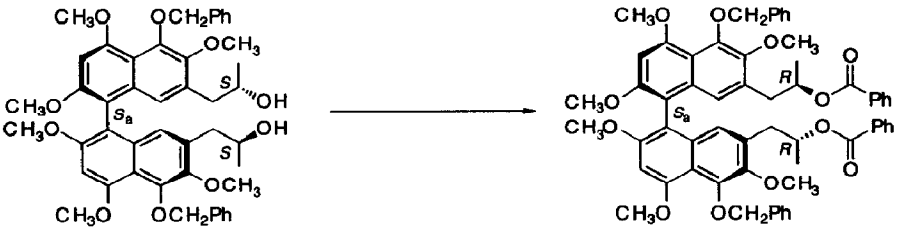
ABSTRACT *Mitsunobu inversion of 1,1'-binaphthalenediol **3** with benzoic acid was studied, and the success of the reaction was found to depend upon quantitative formation of bis-oxyphosphonium salt **6** at –23 °C, prior to S_N2 displacement at 25 °C.*

During the course of our syntheses of the perylenequinone natural products phleichrome (**1**) and calphostin A (**2**),[2] we required an effective protocol for inversion of the stereogenic 2-hydroxy-1-propyl side-chains from the (*S*)-configuration characteristic of phleichrome (**1**) to the (*R*)-configuration of the calphostins (**2**). A key transformation in our synthesis was the atropdiastereoselective Cu(I)-promoted biaryl coupling reaction[3] of an enantiomerically pure (2*S*)-(2-hydroxy-1-propyl)naphthalene to the corresponding axially chiral 1,1'-binaphthalene system. We observed that the absolute configuration of the (*S*)-stereogenic center of the naphthalene precursor dictated–with useful levels of diastereoselectivity–the *absolute* sense (S_a) of the newly formed stereogenic axis, which was required for the synthesis of *both* phleichrome and the calphostins. Consequently, the seemingly obvious solution of using the enantiomeric (*R*)-naphthalene in the biaryl coupling reaction for synthesis of the calphostins was not an option.

phleichrome (S,S_a,S)-1 calphostin A (R,S_a,R)-2

Ideally, double inversion of the side-chain diols of phleichrome (**1**) could be achieved with *concomitant introduction* of the benzoyl appendages of calphostin A (**2**) using a Mitsunobu reaction[4] or by S_N2 displacement of the corresponding methanesulfonate or trifluoromethanesulfonate esters with potassium benzoate. Under the standard Mitsunobu conditions [benzoic acid, Ph_3P, *i*-PrO_2C–N=N–CO_2*i*-Pr (DIAD), 25 °C], the starting diol was recovered unchanged.[5] Similarly, treatment of the mesylate or triflate with potassium benzoate was unsuccessful. Warming these reaction mixtures above 80 °C lead to isomerization about the stereogenic axis. This failure to effect diol inversion within the perylenequinone framework was postulated to arise from side-chain conformational preferences that severely hindered the approach of nucleophiles.[6]

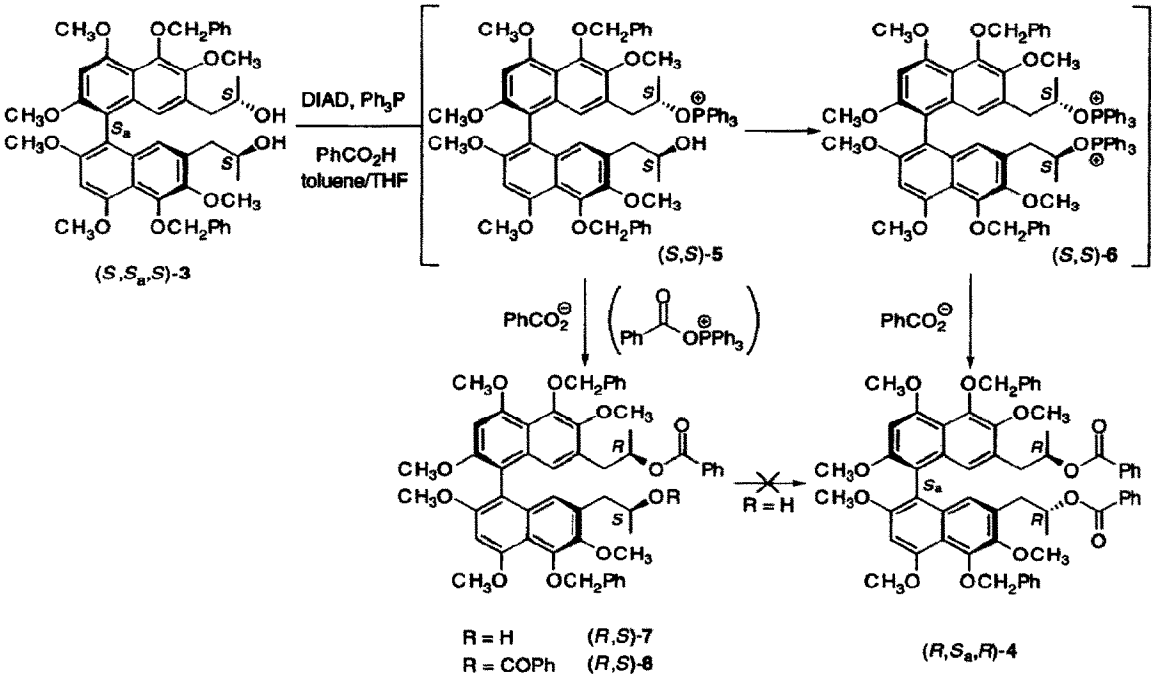
1,1′-Binaphthalenediol **3** appeared to be a more suitable candidate for double inversion of the (2*S*)-hydroxypropyl side-chains. Compared to perylenequinones such as **1** or **2**, the side-chains of **3** are more accessible, being capable of independent rotation. Furthermore, **3** was not prone to thermally induced isomerization about the stereogenic axis. Diol **3** was the earliest intermediate from which *both* phleichrome (**1**) and calphostin A (**2**) could be prepared, being the first compound in the synthetic pathway that possessed the correct (S_a)-stereogenic axis.



(*S*,S_a,*S*)-**3** (*R*,S_a,*R*)-**4**

Subjecting diol **3** to standard Mitsunobu conditions at 25 °C did not provide the doubly inverted binaphthalene diester **4**, but instead afforded the mono-inverted ester **7**. The failure to form **4** was attributed to steric hindrance by the inverted, esterified alcohol in **7**, where the ester either prevented formation of the second oxyphosphonium salt, thereby stopping the reaction at intermediate **7**, or it prevented attack of the benzoate nucleophile on the already formed oxyphosphonium salt of **7** (R = P^+Ph_3), which underwent hydrolysis back to the alcohol **7** upon workup. Resubjection of **7** to the above conditions did not provide the doubly inverted diester **4**.

The mechanism and kinetics of the Mitsunobu reaction have been studied in detail by Hughes, *et al.*,[7] who found that the rate of S_N2-displacement versus alcohol activation varied with the concentration of protonated and deprotonated carboxylic acid (RCO_2H/RCO_2^-). When the ratio of RCO_2H/RCO_2^- was ≤ 1:1, S_N2 displacement was rate determining, and when the ratio was ≥ 3:1, alcohol activation became rate determining. On the basis of our results and on the work of Hughes, *et al.*,[7] we felt that if the bis-oxyphosphonium salt **6** could be formed quantitatively *before* S_N2-displacement, then the subsequent double inversion could be achieved.



A solution of 1,1′-binaphthalene **3**, Ph_3P (2.5 equiv per hydroxyl), and benzoic acid (3 equiv per hydroxyl) in a mixture of toluene/THF (10:1) at –23 °C ($CO_{2(s)}/CCl_4$) was treated with DIAD, and the reaction was allowed to stir for 1 h at –23 °C and then at 25 °C. This procedure provided a 2:1 ratio of doubly inverted diester **4** to single inverted diester **8**, after careful chromatographic purification.[8] Upon variation of the reaction conditions, the formation of **4** was found to depend principally upon two variables: the time the reaction mixture spent at –23 °C and the polarity of the solvent.[9] Increasing the time the reaction was maintained at –23 °C from 1 to 3 h and

increasing the proportion of THF from 10 to 50% proved to be optimal for the formation of **4**. Under these conditions, 1,1'-binaphthalene diester **4** was isolated in a synthetically useful 46% yield, with much of remainder of the material isolated consisting of elimination by-products.[10]

The low-temperature (–23 °C) modification of the Mitsunobu inversion reaction described herein effected the desired transformation in useful yields. Our results suggest that incomplete formation of the second oxyphosphonium salt (**5** → **6**) was the reason for failure of standard, room temperature Mitsunobu reaction conditions.

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1. (a) Genentech Investigator in Biomolecular Chemistry (1990-1992). (b) Recipient of a Dreyfus Foundation Distinguished New Faculty Award (1989-1994), an American Cancer Society Junior Faculty Research Award (1990-1993), and the American Cyanamid Young Faculty Award (1993-1996).
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5. Our prerequisite of direct introduction of the benzoate esters of calphostin A *concomitant* with inversion of the stereogenic centers ruled out the use of more acidic carboxylic acids that have been shown to participate with greater efficacy in Mitsunobu reactions of hindered secondary alcohols. For these modifications, see: (a) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*. 3017.
6. For a review on perylenequinones, see: Weiss, U.; Merlini, L.; Nasini, G. *Prog. Chem. Org. Nat. Prod.* **1987**, *52*, 1. The side-chains of substituted perylenequinones are substantially restricted in their ability to rotate independent of one another because of the helical twist of the rigid perylene ring system.
7. Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.
8. Diester **8** presumably arises by formation of mono-oxyphosphonium salt **5**, displacement to afford **7**, followed by acylation via a phosphonium-activated carboxylate.
9. At –23 °C, toluene was found to cause solubility problems (*i.e.*, precipitation of **5** or **6** occurred) during attempted formation of bis-oxyphosphonium salt **6**.
10. Olefinic by-products were formed in significant amounts in all displacement reactions of these homobenzylic alcohols.

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