Palladium-Catalyzed Synthesis of *trans*-2,5-Diaryltetrahydrofurans, Potent Platelet-Activating Factor Antagonists

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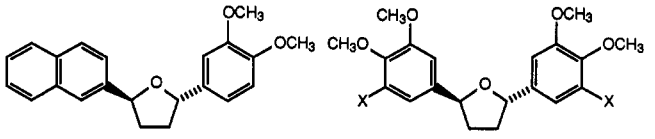
Summary: *trans*-2,5-Diaryltetrahydrofurans **1–3**, potent platelet-activating factor antagonists, have been synthesized regio- and stereoselectively by a three-step approach involving sequential palladium-catalyzed diarylation of 2,3-dihydrofuran and subsequent hydrogenation.

Platelet-activating factor (PAF) has been identified as 1-*O*-hexadecyl/octadecyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine.[1] PAF is synthesized and secreted by a variety of cells involved in inflammatory responses, including basophils, neutrophils, platelets, macrophages, endothial cells, and IgE-sensitized bone marrow mast cells.[2] PAF is linked to a variety of biological actions,[3] including inter alia smooth muscle contraction, neutrophil degranulation, platelet aggregation and cardiac, renal, and gastrointestinal dysfunction.[4,5]

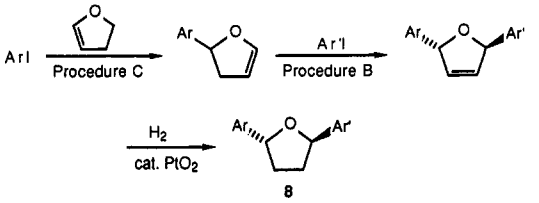
A number of PAF antagonists are known, including various PAF structural analogues, ginkgolides, triazolobenzodiazepines, benzofuranoid neolignans, and furanoid lignans.[6] Recently, a number of *trans*-2,5-diaryltetrahydrofurans,[7-11] particularly *trans*-2-(3,4-dimethoxyphenyl)-5-(2-naphthyl)tetrahydrofuran (**1**),[8,9] *trans*-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofuran (**2**),[7-9] and *trans*-2,5-bis(3,4,5-trimethoxyphenyl)tetrahydrofuran (**3**),[7,8]



1 **2**, R = H; **3**, R = CH_3O

have been synthesized and their anti-PAF activities evaluated.[12,13] Enantioselective syntheses of compounds **1** and **2** have also recently been reported, and both enantiomers have been observed to be about equally biologically active.[12] All previous syntheses have involved a number of synthetic steps, frequently proceed in low overall yield, and/or afford a mixture of cis and trans isomers. The cis isomers are essentially biologically inactive.[11,12] Recent work on the synthesis of carbon analogues of these diaryltetrahydrofurans involving the palladium-catalyzed diarylation of cyclopentene[14] prompts us to report our work on the synthesis of the very important tetrahydrofurans **1–3** using an approach involving sequential palladium-catalyzed diarylation of 2,3-dihydrofuran and subsequent hydrogenation.

Scheme I



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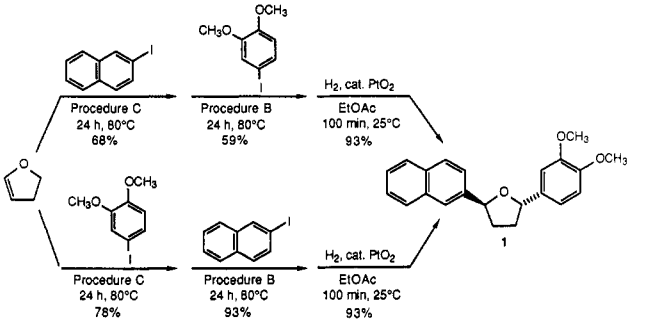
Scheme II



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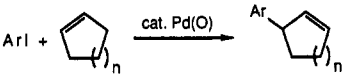
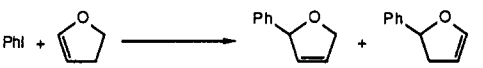
We have recently reported a convenient palladium-catalyzed procedure for cross-coupling aryl iodides and cyclic alkenes (eq 1).[15] The use of 2.5% $Pd(OAc)_2$, 1 equiv



(1)

of *n*-Bu_4NCl, and 3 equiv of KOAc in DMF at room temperature or 80 °C (procedure A) generally gives excellent yields, but subsequent work revealed that certain cyclic alkenes, particularly cyclic ethers, afforded mixtures of regioisomers and a number of important organic functional groups in the aryl iodide could not be accommodated by this procedure (eq 2).[16] As a result, we developed two alternate procedures: procedure B[16,17] (3–4% $Pd(OAc)_2$,



Procedure	4 %	5 %
A	53	27
B	98	—
C	—	76

(2)

(1) Hanahan, D. J. *J. Biol. Chem.* **1980**, *255*, 5514.
(2) Benveniste, J.; Arnoux, A. *Platelet-Activating Factor and Structurally Related Ether-Lipids*; Inserm Symposium No. 23; Elsevier Science: Amsterdam, 1983.
(3) Hanahan, D. J. *Ann. Rev. Biochem.* **1986**, *55*, 483.
(4) Rosam, A. C.; Wallace, J. L.; Whittle, B. J. R. *Nature* **1986**, *319*, 54.
(5) Blank, M. L.; Synder, F.; Byers, L. W.; Brooks, B.; Muirhead, E. E. *Biochem. Biophys. Res. Commun.* **1979**, *90*, 1194.
(6) Braquet, P. *Drugs Future* **1987**, *12*, 643.
(7) Biftu, T.; Gamble, N. F.; Doebber, T.; Hwang, S.-B.; Shen, T.-Y.; Snyder, J.; Springer, J. P.; Stevenson, R. *J. Med. Chem.* **1986**, *28*, 1917.
(8) Biftu, T.; Hwang, S.-B.; Doebber, T. W.; Beattie, T. R.; Shen, T.-Y. U.S. Pat. 4,539,332; *Chem. Abstr.* **1985**, *104*, 5761z.
(9) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(10) Pompipom, M. M.; Hwang, S.-B.; Doebber, T. W.; Acton, J. J.; Alberts, A. W.; Biftu, T.; Brooker, D. R.; Bugianesi, R. L.; Chabala, J. C.; Gamble, N. L.; Graham, D. W.; Lam, M.-H.; Wu, M. S. *Biochem. Biophys. Res. Commun.* **1988**, *150*, 1213.
(11) Pompipom, M. M.; Bugianesi, R. L. U.K. Pat. Appl. 8,726,509; *Chem. Abstr.* **1988**, *110*, 8029*b*.
(12) Corey, E. J.; Chen, C.-P.; Parry, M. J. *Tetrahedron Lett.* **1988**, *29*, 2899.
(13) Hwang, S.-B.; Lam, M.-H.; Biftu, T.; Beattie, T. R.; Shen, T.-Y. *J. Biol. Chem.* **1985**, *260*, 15639.
(14) Prashad, M.; Tomesch, J. C.; Wareing, J. R.; Smith, H. C.; Cheon, S. H. *Tetrahedron Lett.* **1989**, *30*, 2877.
(15) Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* **1988**, *29*, 905.
(16) Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603.
(17) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

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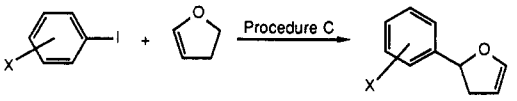
9% Ph_3P, 2 equiv of Ag_2CO_3, CH_3CN as the solvent, 80 °C) and procedure C[16] (same as procedure A, but add 2.5% Ph_3P). When procedure B was applied to the reaction of iodobenzene and 2,3-dihydrofuran, only compound **4** was obtained in 98% yield. Most interestingly, the same reaction employing procedure C gave only compound **5** in 76% isolated yield. Indeed, procedure C has proven general for the cross-coupling of a wide variety of aryl iodides and 2,3-dihydrofuran (eq 3).



(3)

X = p-CO_2Et (76%), o-NO_2 (61%), o-CHO (53%), o-MeO (53%, 3 days reaction time)

These exciting results suggested the extremely efficient approach to *trans*-2,5-diaryltetrahydrofurans outlined in Scheme I. The success of that effort is hereby communicated.

We first examined the synthesis of the unsymmetrical diaryltetrahydrofuran **1**. Arylation of 2,3-dihydrofuran using procedure C and 2-iodonaphthalene, followed by arylation using procedure B and 1,2-dimethoxy-4-iodobenzene, and subsequent hydrogenation over a PtO_2 catalyst afforded the desired PAF antagonist **1** in 37% overall yield. A significantly improved 67% overall yield was obtained by reversing the arylation sequence (Scheme II).

While the first arylation step is usually run using a 5-fold excess of cheap, commercially available 2,3-dihydrofuran, the second step is carried out employing a 1:1 ratio of cyclic alkene and aryl iodide. Nevertheless, excellent overall yields are obtained. Furthermore, the stereochemistry of the final product from either sequence was observed to be pure trans.[18] This sequence is, therefore, the only one so far published which gives exclusively the desired trans isomer.

Analogous sequences were carried out to prepare symmetrical compounds **2** and **3**. Thus, 2,3-dihydrofuran and 1,2-dimethoxy-4-iodobenzene underwent smooth arylation (procedure C, 78%; procedure B, 82%) and hydrogenation (60 min, 69%) to afford PAF antagonist **2** in 44% overall yield. Similarly, 1,2,3-trimethoxy-5-iodobenzene (procedure C, 63%; procedure B, 56%; hydrogenation 30 min, 78%) afforded diaryltetrahydrofuran **3** in 28% overall yield. In general, the more electron-rich the aryl iodide, the lower the yield of arylated product. Again pure trans products were obtained exclusively.[18] Our initial attempts to effect both arylation steps in one pot have so far provided only complex mixtures of arylated products.

In summary, a new, highly efficient palladium-catalyzed approach from 2,3-dihydrofuran and simple aryl iodides to potent PAF antagonist *trans*-2,5-diaryltetrahydrofurans has been developed. The process is extremely versatile, the overall yields are high, and only the biologically active trans product is formed.

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(18) Stereochemistry was assigned by comparing the ^1H NMR spectral data for compounds **1** and **2** to the data generously supplied by Professor E. J. Corey.

Asymmetric Synthesis of 3-Substituted 2-*exo*-Methylenecyclohexanones via 1,5-Diastereoselection by Using a Chiral Amine

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Summary: (*S*)-2-((2-(Methoxymethyl)-1-pyrrolidinyl)-methyl)-2-cyclohexen-1-one (**2**) underwent asymmetric conjugate addition of R_2CuLi in the presence of $ZnBr_2$, followed by elimination of the chiral auxiliary pyrrolidine, to produce the optically active 3-substituted 2-*exo*-methylenecyclohexanones (**3**) in 90% ee.

Most asymmetric induction with chiral auxiliaries involves a stereodifferentiating reaction that affords a diastereomer as the primary product, from which the used auxiliary must be removed to obtain the desired enantiomer.[4] On the other hand, the asymmetric reaction using a chiral leaving group should produce the enantiomer directly, but very few attempts have succeeded in this strategy.[5,6] We have recently found a new synthetic method for 3-substituted 2-*exo*-methylenecycloalkanones from 2-(nitromethyl)cycloalkenones such as **1** by conjugate addition of organocuprates followed by elimination of the nitro group.[7] In this context, we aimed to develop an asymmetric synthesis utilizing this type of reaction and focused our attention on employing chiral amines in place of nitro group. The designed substrate **2** could be easily prepared by our method[8] and gave enantiomerically enriched 2-*exo*-methylenecycloalkanones by the action of organocopper reagents.[9] Here we report a novel diast-

(1) Ehime University.
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(4) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic Press: New York, 1983 and 1984; Vols. 2 and 3.

(5) For rare examples of addition-elimination type of asymmetric induction reactions using chiral leaving groups, see: (a) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881. (b) Wilson, J. M.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930. (c) Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Terada, S. *J. Am. Chem. Soc.* **1986**, *108*, 3855.
(6) For S_N type of asymmetric induction reactions using chiral leaving groups, see: references cited in ref 5c.
(7) Tamura, R.; Tamai, S.; Katayama, H.; Suzuki, H. *Tetrahedron Lett.* **1989**, *30*, 3685.
(8) Tamura, R.; Tamai, S.; Suzuki, H. *Tetrahedron Lett.* **1989**, *30*, 2413.

0022-3263/90/1955-0408$02.50/0