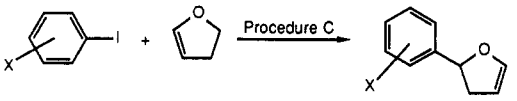
9% Ph_3P, 2 equiv of Ag_2CO_3, CH_3CN as the solvent, 80 °C) and procedure C[16] (same as procedure A, but add 2.5% Ph_3P). When procedure B was applied to the reaction of iodobenzene and 2,3-dihydrofuran, only compound **4** was obtained in 98% yield. Most interestingly, the same reaction employing 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.
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(8) Tamura, R.; Tamai, S.; Suzuki, H. *Tetrahedron Lett.* **1989**, *30*, 2413.

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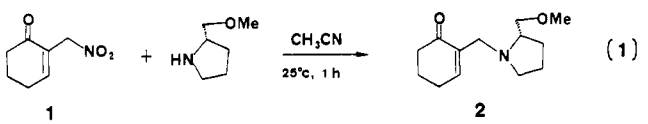
Table I. Asymmetric Synthesis of 3-Substituted 2-*exo*-Methylenecyclohexanones (eq 2)

		3			4				
entry	RM		yield, %	config		yield,[a] %	t/c[b]	% ee[c]	config[d]
1	Me_2CuLi	**3a**	84	*S*[e]	**4a**	59	97/3	90	2*S*,3*S*[f]
2[g]	Me_2CuLi		–		**4a**	31	97/3	90	2*S*,3*S*
3	n-Bu_2CuLi	**3b**	87	*S*[h]	**4b**	72	96/4	90	2*S*,3*S*[i]
4[g]	n-Bu_2CuLi		–		**4b**	44	96/4	90	2*S*,3*S*
5	n-$Bu_2CuMgCl$		–		**4b**	53	93/7	20	2*S*,3*S*
6	n-BuMgCl		–		**4b**	26	95/5	26	2*R*,3*R*
7	Et_2CuLi	**3c**	82	*S*[j]	**4c**	45	93/7	90	2*S*,3*S*[k]
8	$Et_2CuMgBr$		–		**4c**	72	93/7	62	2*S*,3*S*
9	$(vinyl)_2CuLi$	**3d**[l]	–		**4d**	32	95/5	86[m]	2*R*,3*R*[n]
10[g]	$(vinyl)_2CuLi$		–		**4d**	–[o]			
11	$(vinyl)_2CuMgBr$		–		**4d**	48	95/5	22[m]	2*S*,3*S*
12	Ph_2CuLi	**3e**[l]	–		**4e**	42	53/47	92	2*R*,3*R*[p]
								90	2*S*,3*R*[p]

[a] Overall isolated yield. [b] Trans/cis determined by capillary GLC. [c] Determined by HPLC analysis with a chiral column (Daicel Chiralcel OJ, hexane/2-propanol, 9:1). [d] Referred to the trans isomer unless otherwise noted. The enantiomeric purity of the cis isomer was comparably high, although it was not accurately determined by HPLC analysis. [e] $[\alpha]_D$ +32.3° (*c* 1.00, $CHCl_3$). [f] $[\alpha]_D$ –11.0 (*c* 1.64, $CHCl_3$). [g] Without $ZnBr_2$. [h] $[\alpha]_D$ +33.0° (*c* 2.74, $CHCl_3$). [i] $[\alpha]_D$ –21.9° (*c* 1.14, $CHCl_3$). [j] $[\alpha]_D$ +40.8° (*c* 1.94, $CHCl_3$). [k] $[\alpha]_D$ –19.0° (*c* 1.62, $CHCl_3$). [l] Unable to be isolated. [m] Determined after conversion to **4c** upon hydrogenation (H_2, Pd–C). [n] $[\alpha]_D$ –38.8° (*c* 1.30, $CHCl_3$). [o] A trace amount. [p] Tentatively assigned. See the text.

ereodifferentiating addition–elimination reaction involving 1,5-transfer of stereogenicity[10] that directly leads to an enantiomer.

(*S*)-2-((2-(Methoxymethyl)-1-pyrrolidinyl)methyl)-2-cyclohexen-1-one (**2**) was prepared in 89–94% yield from 2-(nitromethyl)-2-cyclohexen-1-one (**1**) and (*S*)-2-(methoxymethyl)pyrrolidine[11] (eq 1).[8] In the presence of $ZnBr_2$,

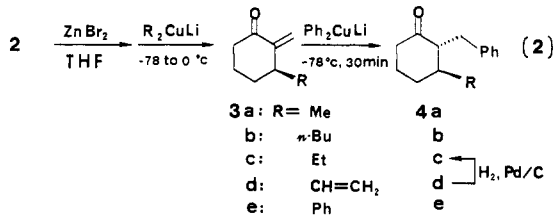


(1)

1 **2**

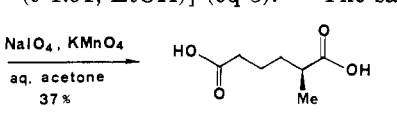
2 underwent asymmetric conjugate addition of lithium diorganocuprates, followed by elimination of the pyrrolidine upon aqueous workup,[12] to produce the optically active 3-substituted 2-*exo*-methylenecyclohexanones (**3**) in 90% enantiomeric excess (ee) as shown in eq 2 and Table I.[13]

The ee of **3** was determined by HPLC analysis of the corresponding **4**, derived by addition of 1.5 equiv of Ph_2CuLi (eq 2), with a chiral stationary phase column

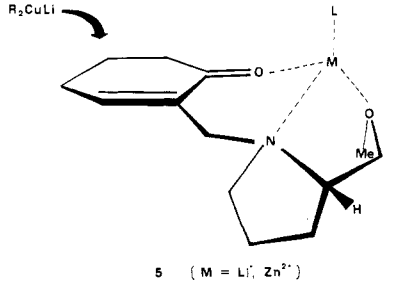


(2)

(Daicel Chiralcel OJ), since it was impossible to directly determine its enantiomeric purity by any chromatographic technique. The *S* configuration of (+)-**3a** (R = Me) was unequivocally established by oxidation of it into (*S*)-(+)-2-methyladipic acid, $[\alpha]_D$ +13.2° (*c* 0.60, EtOH) [lit.[14] $[\alpha]_D$ +13.8° (*c* 1.91, EtOH)] (eq 3).[15] The same *S* configuration was assigned to **3b** (R = *n*-Bu) and **3c** (R = Et) by comparison of the CD spectra of **4b** ($[\theta]_{295}$ –4850 deg cm^2 $dmol^{-1}$ in acetonitrile) and **4c** (–3290) with that of (2*S*,3*S*)-(–)-**4a** (–3990) derived from (*S*)-**3a**. Due to the instability of **3d** (R = vinyl) and **3e** (R = Ph), the crude materials were directly transformed into **4d** and **4e**. The *R* configuration and 86% ee for **3d** were established upon hydrogenation (H_2, Pd/C) of **4d** into (2*S*,3*S*)-(–)-**4c**, which was subjected to HPLC analysis (Table I, entry 9). Diphenyl derivative **4e** was a 53:47 mixture of trans and cis isomers;[16] the enantiomeric purity of each isomer was determined to be 92 (trans) and 90% ee (cis) by HPLC analysis (entry 12). Based on the HPLC behavior of **4e**, as well as the transition-state model **5** (vide infra), the 2*R*,3*R* and 2*S*,3*R* configurations were tentatively assigned to *trans*-**4e** and *cis*-**4e**, respectively. The yields of **4** in Table I show overall isolated ones from **2** and correspond to a variation of the yields of **3**, since addition of Ph_2CuLi to **3** gives **4** in high yields.



(3)



5 (M = Li, Zn^{2+})

(9) A 2-((diethylamino)methyl)cyclopentenone derivative has been shown to undergo conjugate addition of an alkenylcuprate to directly give the corresponding 2-*exo*-methylenecyclopentanone, see: Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.* **1988**, *53*, 5590.

(10) For examples of 1,5-stereocontrol, see: Uemura, M.; Minami, T.; Hirotsu, K.; Hayashi, Y. *J. Org. Chem.* **1989**, *54*, 469 and ref 2 cited therein.

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(12) Elimination of the chiral leaving group is likely to occur at the stage of aqueous workup, see: ref 5c and 9.

(13) A typical experimental procedure for asymmetric conjugate addition–elimination reaction follows: A mixture of **2** (1.0 mmol) and $ZnBr_2$ (1.2 mmol) in THF (5 mL) was stirred at 25 °C for 10 min and cooled to –78 °C. n-Bu_2CuLi (2.0 mmol), prepared in a mixed solvent of THF (10 mL) and hexane (ca. 4 mL) from CuBr·Me_2S and *n*-BuLi, was added dropwise at –78 °C. The resulting mixture was slowly allowed to warm to 0 °C over ca. 1 h, and then saturated aqueous NH_4Cl (10 mL) was added. After usual extraction with ether, crude product **3b** was purified by florisil column chromatography (Et_2O).

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(15) Lemieux, R. U.; von Rudloff, E. *Can. J. Chem.* **1955**, *33*, 1701, 1710. In the present experiment, 1 equiv of $NaIO_4$ and 5 equiv of $KMnO_4$ were used in aqueous acetone without base.

(16) The ratios of trans vs cis of **4** in Table I reflect kinetic protonation of metal enolate intermediates from **3** and Ph_2CuLi. Generally 2-substituted 3-phenylcyclohexanones showed low kinetic selectivity.

Features of the asymmetric synthesis of 3-substituted 2-*exo*-methylenecyclohexanones described here are summarized below. (1) Consistently high enantiomeric purity (ca. 90% ee) of **4** was realized as long as R_2CuLi was employed (Table I, entries 1, 3, 7, and 9), although slightly low ee (86% ee) was observed in the reaction with $(vinyl)_2CuLi$ (entry 9). Generally, the absence of $ZnBr_2$ did not affect the ee of **4** but decreased the yields of **4** or **3** to a great extent (entries 2, 4, and 10). (2) Considerable decrease of ee of **4** was noted in the reaction with R_2CuMgX (entries 5, 8, and 11). The use of *n*-BuMgCl even reversed the absolute configuration of **3b**, giving rise to (*R*)-**3b**, as did that of $(vinyl)_2CuMgBr$ (entries 6 and 11).

From these results, one plausible transition-state model can be proposed. The added Zn^{2+} or in situ generated Li^+ [17] should serve to fix the conformation of **2** by coordination to the three hetero atoms in **2**,[18] eventually shielding the *re*-face of **2** partially as illustrated in a metal-chelated conformer **5**. Due to the steric bulk of dimeric R_2CuLi complex, its addition to **5** occurred from the less hindered *si*-face,[19,20] leading to the (*S*)-(+)-**3** (R = Me, Et, *n*-Bu) and (*R*)-**3** (R = vinyl, Ph) enantiomers.[21] The use of (*R*)-**2**, as expected, resulted in the formation of the corresponding antipodal (*R*)-(−)-**3b** having the same 90% ee by reacting with *n*-Bu_2CuLi in the presence of $ZnBr_2$.

The decrease of product ee with R_2CuMgX may mainly arise from the addition of R_2CuMgX or the equilibrating counterpart RMgX to Mg^{2+}-chelated **2**, presumably taking a geometry different from **5**;[18] this reaction should yield (*R*)-**3b** (entry 6) and compete with that of R_2CuMgX complexes to **5**.

This method for optically active 3-substituted 2-*exo*-methylenecyclohexanones constitutes a new direct and simple approach to the synthesis of this important class of compounds.[22] Further, this approach provides ready access to enantiomerically enriched 2-substituted adipic acids (eq 3). Further studies using analogous 5- or 7-membered substrates as well as other nucleophiles are under investigation.

(17) LiBr was present in the reaction with R_2CuLi, since R_2CuLi was prepared from $CuBr \cdot Me_2S$ and RLi in situ.

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(19) For an excellent work on a similar diastereodifferentiating asymmetric conjugate addition using metal chelation to produce 3-substituted cycloalkanones, see: (a) Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *J. Am. Chem. Soc.* **1982**, *104*, 4180. (b) Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, p 225. (c) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72.

(20) For enantioselective conjugate addition reactions of chiral cuprates to 2-cycloalkenones, see: (a) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114. (b) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040. (c) Yamamoto, K.; Kanoh, M.; Yamamoto, N.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 6347.

(21) As an alternative possibility, one reviewer suggested that the cuprate reagent might be directed to the alkene by coordination to the nitrogen and oxygen of the chiral auxiliary via a complex-induced proximity effect: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. We will investigate the source of the observed 1,5-stereocontrol in detail by changing Lewis acids, chiral amines, and nucleophiles and report these results in due course.

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Periodinane Oxidation, Selective Primary Deprotection, and Remarkably Stereoselective Reduction of *tert*-Butyldimethylsilyl-Protected Ribonucleosides. Synthesis of 9-(β-D-Xylofuranosyl)adenine or 3′-Deuterioadenosine from Adenosine[1]

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Summary: Treatment of 9-(2,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl)adenine (**2**) with sodium triacetoxyborohydride in acetic acid and deprotection gave adenosine (**1b**) and 9-(β-D-xylofuranosyl)adenine (**3**) [3:97 (1:32)]. Selective O5′ deprotection of **2**, and hydroxyl-directed reduction with the hydride (or deuteride) reagent gave **1b** (or 3′-deuterio, **1c**) and **3** [99.5:0.5 (199:1)] after deprotection.

Reduction of protected 2′- and 3′-ketonucleoside derivatives with sodium borohydride/alcohol affords epimeric mixtures of the corresponding nucleoside alcohols with stereoselectivity enhanced by proximity to the heterocyclic base.[2] Attack by hydride occurs predominantly at the α-face of the sugar ring trans to the base and with greater stereodifferentiation at the proximal 2′-position. Thus, reduction of 2′-ketonucleoside derivatives gives stereoselectivities of 82–95% for the arabino epimers, whereas analogous treatment of 3′-ketonucleosides gives lower selectivities for the xylo products.[2-4] We now describe remarkable stereocontrol for the synthesis of either the ribo or xylo diastereomers with sodium triacetoxyborohydride in acetic acid beginning with a common 3′-ketonucleoside intermediate.

Sodium triacetoxyborohydride is a mild reducing agent formed by addition of sodium borohydride to an excess of cold acetic acid.[5] This reagent gave chemoselective reduction of aldehydes in the presence of ketones[5a,6] and later was found to effect stereoselective reduction of cyclic[7] and acyclic[6,8] β-hydroxy ketones to the respective trans and anti

(1) This paper is Nucleic Acid Related Compounds. 58. For the previous paper in this series, see: Robins, M. J.; Wood, S. G.; Dalley, N. K.; Herdewijn, P.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 1763.

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