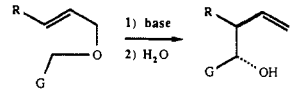
# Enantioselective Synthesis of Macrocyclic Propargylic Alcohols by [2,3] Wittig Ring Contraction. Synthesis of (+)-Aristolactone and Cembranoid Precursors

**James A. Marshall* and Jacques Lebreton**

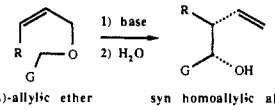
*Contribution from the Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208.* *Received August 24, 1987*

**Abstract:** The use of chiral lithium amide bases to initiate enantioselective [2,3] Wittig rearrangements of allylic ethers was investigated. The 13-membered propargylic ether **1**, a nonresolvable racemate, afforded the 10-membered propargylic alcohol **SS2** in 60–80% ee and 70–85% yield upon treatment with lithium bis[(*S*)-1-phenylethyl]amide in THF at −70 to −15 °C. The enantiomeric base lithium bis[(*R*)-1-phenylethyl]amide afforded the enantiomeric alcohol **RR2** in comparable yield and ee under the same reaction conditions. Alcohol **SS2** was converted to (+)-aristolactone (**RS14**) in a four-step sequence involving Mitsunobu inversion, saponification, hydroalanation–iodination, and carbonylation. The 17-membered propargylic ether **15** also underwent [2,3] Wittig ring contraction upon treatment with the foregoing chiral bases. For this rearrangement, pentane–THF (9:1) was the best solvent. A 7:3 mixture of anti and syn diastereoisomers **16** and **18** was produced, the former with an ee of ca. 30% and the latter with negligible ee. Several acyclic allylic ethers were also examined, but only racemic rearrangement products were formed.

The [2,3] sigmatropic rearrangement of allylic ether $\alpha'$-carbanions, generally known as the "[2,3] Wittig rearrangement", has been the focus of considerable contemporary study.[1] As a rule, rearrangements involving propargylic *E* allylic ethers afford anti homoallylic alcohols (eq 1) and those of *Z* allylic ethers yield syn isomers (eq 2), although exceptions are known.[1,2]

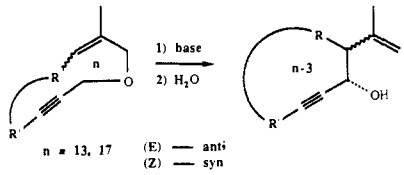



(E)-allylic ether anti homoallylic alcohol (1)




(Z)-allylic ether syn homoallylic alcohol (2)

We recently found that macrocyclic allylic propargylic ethers, upon base treatment at −78 to −40 °C, rearrange to ring-contracted propargylic alcohol products with moderate to excellent stereoselectivity and complete regioselectivity.[3] The one isomeric pair studied showed the expected *E* → anti and *Z* → syn stereoselectivity (eq 3).[3b]




n = 13, 17 (E) — anti (Z) — syn (3)

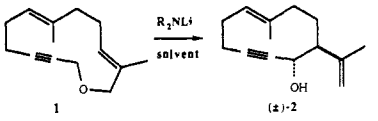
Although the foregoing "[2,3] Wittig ring contractions" exhibit high diastereoselectivity, they lead to racemic products and are therefore not well suited to natural product synthesis. Possible solutions to this problem include the following. (1) Introduction of a "disposable" element at the $\alpha$ position of the allylic ether, thereby creating a stereogenic center capable of exerting stereocontrol in the rearrangement.[4] This strategy has been employed successfully in the ester enolate Claisen rearrangement.[5] However, its implementation would require optical resolution or enantioselective synthesis of the rearrangement precursor. (2) The use of a disposable chiral auxiliary. This approach, recently reported for [2,3] Wittig rearrangements of esters and amides incorporating chiral alcohols and amines as auxiliaries, shows excellent promise.[6] Unfortunately, the rearrangements of interest to us employ achiral alkynyl groupings as anion stabilizers. (3) The use of a chiral base to effect enantioselective deprotonation of the propargylic enantiotopic hydrogens. This approach is appealing because of its operational simplicity and its potential applicability to any of the various [2,3] Wittig substrates. To date, only a few studies of enantioselective deprotonations have been reported, and none of these has involved [2,3] rearrangements.[7] We were encouraged to pursue this line of investigation by Whitesell's seminal work on epoxide eliminations[7a] and the subsequent variations of Asami[7b] in which metalated chiral dialkylamides were found to effect enantioselective deprotonation of weakly acidic enantiotopic protons.

The 13-membered propargylic allylic ether **1** served as the initial focus of our studies.[3c] We had previously utilized this ether in a total synthesis of the sesquiterpene lactone (±)-aristolactone using *n*-BuLi to initiate a facile [2,3] Wittig ring contraction to the racemic *anti*-2-isopropenyl-9-cyclodecyn-1-ol, (±)-**2**.[3b] In the present effort we were interested in using a chiral amide base in the hope of differentiating the propargylic methylene protons $H_a$ and $H_b$ of ether I (Scheme I).[8] Following this, an enantioselective rearrangement might take place provided one or more of the following conditions were met: (1) concerted carbon–carbon bond formation without the intervention of a free carbanion, (2) for-

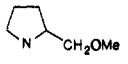
(1) For a recent comprehensive review, see: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.
(2) Cf. Mikami, K.; Azuma, K.; Nakai, T. *Chem. Lett.* **1983**, 1379; *Tetrahedron* **1984**, *40*, 2303.
(3) (a) Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 4316. (b) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *Tetrahedron Lett.* **1987**, *28*, 723. (c) Preliminary communication: Marshall, J. A.; Lebreton, J. *Tetrahedron Lett.* **1987**, *28*, 3323.
(4) Cf. Baldwin, J. E.; Patrick, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 3556. Sayo, N.; Azuma, K.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 565. Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1985**, *26*, 5013.
(5) Ireland, R. E.; Varney, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 3668.
(6) Cf. Takahashi, O.; Mikami, K.; Nakai, T. *Chem. Lett.* **1987**, 69. Mikami, K.; Fujimoto, K.; Kasuga, T.; Nakai, T. *Tetrahedron Lett.* **1984**, 25, 6011. Mikami, K.; Takehashi, O.; Kasuga, T.; Nakai, T. *Chem. Lett.* **1985**, 1729.
(7) (a) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755. (b) Asami, M. *Chem. Lett.* **1984**, 829. (c) Hogeveen, H. Kwart, L. *Tetrahedron Lett.* **1982**, *23*, 105. (d) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1986**, *27*, 631. (e) Hogeveen, H.; Menge, W. M. P. B. *Tetrahedron Lett.* **1986**, *27*, 2767. (f) Yamashita, T.; Mitsui, H.; Watanabe, H.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 961. (g) Cain, C. M.; Simpkins, N. S. *Tetrahedron Lett.* **1987**, *28*, 3723.
(8) Actually the cyclic ethers incorporating trans double bonds are nonresolvable racemates. The trans double bond endows them with planar chirality and the combination of ring size and double-bond substituents render them nonresolvable by virtue of jump-rope rotation. Thus the propargylic ether $CH_2$ protons are diastereotopic, but they rapidly interconvert through the aforementioned rotation. Cf. Marshall, J. A.; Audia, V. H.; Jenson, T. M.; Guida, W. C. *Tetrahedron* **1986**, *42*, 1703. In unsubstituted *trans*-cycloalkenes, a bridging chain of six or (presumably) fewer carbons is required to prevent such rotation at room temperature. Cope, A. C.; Banholzer, K.; Keller, H.; Pawson, B. A.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 5157. Binsch, G.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 5157.

0002-7863/88/1510-2925$01.50/0 

**Table I.** [2,3] Wittig Ring Contraction of Ether **1** with Lithium Amide Bases




1 (±)-2

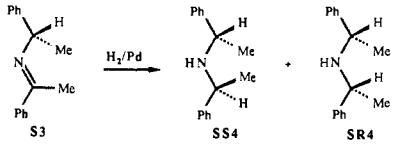
| $R_2N$[a] | solvent | T, °C | t, h | yield, % |
|---|---|---|---|---|
|  | THF | −78 | 1 | *b* |
| | THF | −20 | 3 | dec |
| | pentane | −78 to 20 | 1–12 | *b* |
|  | THF | −78 | 1 | *b* |
| | THF | −78 to 20 | 2.5 | dec |
|  | THF | −78 | 1 | 50 |
|  | THF | −78 | 0.7 | 97 |
| *i*-$Pr_2N$ | THF | −78 | 1.2 | 57 |
| $(PhCHMe)_2N$[d] | THF | −78 to 0 | 2 | 86 |

[a] The amines were purchased from Aldrich Chemical Co., Milwaukee, WI. [b] Only starting material was recovered. [c] Cis/trans mixture. [d] Meso isomer.

mation of a chiral ($sp^3$) anion whose stereogenic inversion would be energetically disfavored because of the macrocyclic ring, (3) formation of a planar anion whose facial orientation relative to the allylic ether double bond would be preserved by a steric barrier to jump-rope rotation,[8] (4) formation of a configurationally stable chiral anion–conjugate acid pair.[7d] Ether **1** fulfilled the prerequisites of conditions 1–3 especially well because of the enforced close proximity of the reacting centers and the relative inflexibility of the macrocyclic ring. In principle, condition 4 could obtain with any propargylic allylic ether.

Before embarking upon the main theme of this study, we conducted a brief survey of amide bases for possible use in the rearrangement. Our findings are summarized in Table I. Best results were obtained with the hindered amides lithium 2,2,6,6-tetramethylpiperidide, lithium diisopropylamide, and lithium bis(1-phenylethyl)amide. The pyrrolidine bases, lithium 2,4-dimethylpyrrolidide (cis/trans mixture) and lithio-2-(methoxymethyl)pyrrolidide, were ineffective at low temperature and caused decomposition of starting material at higher temperature. Lithium 2,6-dimethylpiperidide (cis/trans mixture) was moderately effective. In view of these preliminary findings, we selected lithium bis(1-phenylethyl)amide **4** as the chiral base for subsequent study with several propargylic ethers.

The amine **SS4** was prepared according to Overberger et al. through hydrogenation of the Shiff base **S3** of (*S*)-(−)-1-phenylethylamine and acetophenone (eq 4).[9] The resultant 85:15 mixture of **SS4** and the meso isomer **SR4** were readily separated by factional crystallization of the hydrochlorides from water, as reported. The enantiomeric amine **RR4** was prepared analogously

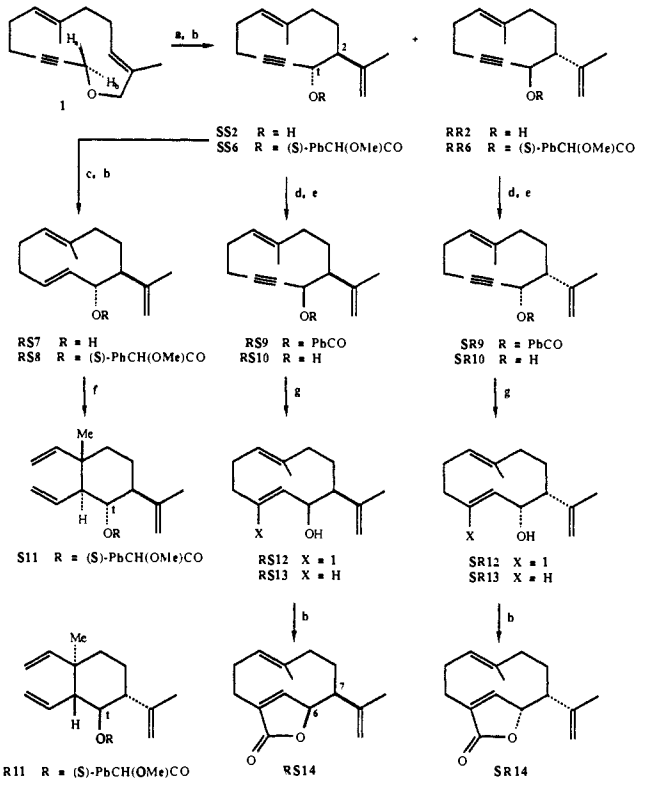



(4)

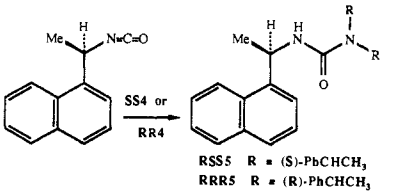
from the Shiff base of (*R*)-(+)-1-phenylethylamine. The amines **SS4** and **RR4** contained none of the meso isomer **SR4** according to capillary GC analysis. The two samples showed opposite and nearly equal rotation, $[\alpha]_D$ −171.6° and +167.6°, respectively, in $CHCl_3$. These rotations were some 15° lower than the absolute value reported for the (−)-enantiomer in unspecified solvent and concentration.[9] Our starting 1-phenylethylamine enantiomers were found to be >98% optically pure through $^1H$ NMR analysis of their crystalline *O*-methylmandelic amide derivatives. Not surprisingly, we were unable to prepare the analogous amides of the secondary amines **SS4** or **RR4**. However, the urea derivatives **RSS5** and **RRR5** were formed quantitatively upon prolonged treatment of the amines with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (eq 5). These derivatives were found to be >95% pure by $^1H$ NMR analysis. Thus, the amines employed in this study are of high optical purity.

(9) Overberger, C. G.; Marullo, N. P.; Hiskey, R. C. *J. Am. Chem. Soc.* **1961**, *83*, 1374. See ref 7c for a correction in assignment of absolute configuration.

**Scheme I**[a]




[a] (a) (*R,R*)- or (*S,S*)-$(PhCHCH_3)_2NLi$, hexane–THF, −40 to −30 °C; (b) (*S*)-PhCH(OMe)$CO_2H$, DCC, DMAP, $CH_2Cl_2$; (c) Red-Al, THF, $H_2O$; (d) $Ph_3P$, DEAD, $PhCO_2H$, $C_6H_6$; (e) KOH, MeOH; (f) $PhCH_3$, reflux; (g) Red-Al, THF, NIS; (h) $(Ph_3P)_2PdCl_2$, $K_2CO_3$, $H_2NNH_2$, THF, CO.




(5)

Upon treatment with a threefold excess of lithio-**SS4** in THF at −70 to −15 °C, ether **1** afforded optically enriched alcohol **2**, $[\alpha]_D$ −32.9°, in 82% yield. Under comparable conditions, use of lithio-**RR4** led to optically enriched alcohol **2** of the opposite rotation, $[\alpha]_D$ +33.4° (Table II). Rearrangement proceeded more slowly in pentane–THF (9:1) and afforded material of lower rotation. In ether the rearrangement was rapid, but enantioselectivity was low. Interestingly, a product of opposite optical rotation was slightly favored in ether vs THF. Lower temperature appeared to enhance enantioselectivity, although this point was not studied in detail. The chiral amide derived from (*S*)-(1-phenylethyl)isopropylamine readily effected rearrangement of ether **1**, but afforded rearranged alcohol **2** of negligible optical rotation.

Support for the absolute configuration of the optically enriched rearrangement products **2** and a preliminary indication of their

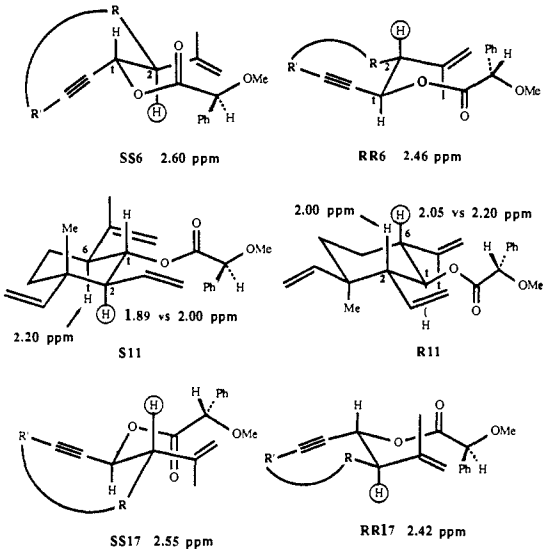
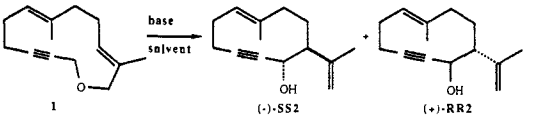



**Figure 1.** Assignments of absolute configuration to [2,3] Wittig products through chemical-shift differences of (*S*)-*O*-methylmandelates.

**Table II.** [2,3] Wittig Ring Contraction of Ether **1** with Lithium (*R*)- and (*S*)-(1-Phenylethyl)amide Bases




| base | solvent | *T*, °C | *t*, min | yield, % | $[\alpha]_D$, deg | ee,[a] % |
|---|---|---|---|---|---|---|
| Li-**SS4** | THF | −70 to −15 | 45 | 82 | −32.9 | 69[b] |
| | 1:9 THF–pentane | −25 to 0 | 90 | 68 | −20.6 | 43 |
| | $Et_2O$ | −25 to −15 | 30 | 70 | +4.2 | 9 |
| *c* | THF | −20 | 60 | 82 | +0.9 | 2 |
| Li-**RR4** | THF | −35 to −25 | 60 | 78 | +33.4 | 70[b] |
| | THF | −20 | 40 | 75 | +28.5 | 60 |

[a] Calculated from the optical rotation of resolved alcohol **SS2** ($[\alpha]_D$ −47.4°). [b] A typical result. Values of 60–80% ee were obtained from comparable runs. [c] (*i*-Pr)[(*S*)-PhCH(Me)]NLi.

optical purity came from $^1$H NMR analysis of the (*S*)-*O*-methylmandelates **SS6** and **RR6**. Trost, Springer, and co-workers have shown that *O*-methylmandelates of secondary alcohols adopt a conformation in which the α (carbinyl) H and the methoxy substituent eclipse the ester carbonyl.[10] Consequently, the phenyl grouping exerts a shielding effect on protons located at the β or β′ position, depending upon absolute configuration. According to this model (Figure 1), the methine proton at C2 in the (*S*)-*O*-methylmandelate **RR6** would expectedly appear upfield from the corresponding proton in mandelate **SS6**.

Conversion of the rearrangement product containing predominantly the (−)-alcohol (**SS2**) to the (*S*)-*O*-methylmandelate according to the procedure of Trost and Springer et al.[10] afforded a mixture of diastereoisomers that could be separated by column chromatography on silica gel. The C2 methine proton appeared at 2.60 ppm in the major and at 2.46 ppm in the minor diastereoisomer. Thus the (−)-alcohol can be assigned the *S,S* configuration. The ratio of the two methine signals as well as those of several others unique to each diastereoisomer was roughly 80:20 in the spectrum of the crude ester mixture. A more accurate evaluation of enantiomeric excess (ee) proved possible by comparing the optical rotation of the crude rearranged alcohols **2** with those of the pure enantiomers. These were secured by saponification of the purified *O*-methylmandelates **SS6** and **RR6**. The resulting alcohols showed essentially equal but opposite optical rotations, −47.4° for **SS2** and +47.1° for **RR2**.

As an added check on these configurational assignments we converted (−)-**SS2** to the dihydro derivative (**RS7**) by treatment with Red-Al (Aldrich) followed by aqueous quench.[11] The $^1$H NMR spectrum of the (*S*)-*O*-methylmandelate (**RS8**) was too complex for accurate analysis owing to the presence of conformational isomers (~70:30) as previously noted for the benzoate derivative of racemic **7**.[3b] However, upon heating in refluxing toluene, mandelate **RS8** smoothly rearranged to the crystalline cyclohexyl isomer **S11**, mp 65–66 °C. The (*S*)-*O*-methylmandelate of the racemic counterpart of **11** (1:1 **S11** and **R11**) was prepared from the racemic alcohol [(±)-**11**, R = H] via the aforementioned benzoate [(±)-**11**, R = PhCO]. The methine protons at C2 and C6 in **S11**/**R11** could be seen as two sets of signals at 1.89, 2.20 and 2.00, 2.05 ppm, respectively, in this mandelate mixture. The mandelate **S11** derived from optically pure material **RS8** showed only the signals at 2.20 and 1.89 ppm. Thus H2 is shielded (1.89 vs 2.00 ppm) in the derivative **S11** whereas H6 is shielded (2.05 vs 2.20 ppm) in the diastereomeric mandelate **R11**. These findings (see Figure 1) are consistent with the assignments already deduced for (−)-**2** as *S,S* and (+)-**2** as *R,R*.

We have previously reported the conversion of racemic alcohol (±)-**2** to racemic aristolactone (±)-**14** by the route pictured in Scheme I.[3b] It was of interest to repeat this synthesis with the resolved materials in order to establish the absolute configuration of natural aristolactone. Accordingly, each of the two alcohols was carried through the sequence to afford the enantiomeric aristolactones **RS14**, mp 110–111 °C, $[\alpha]_D$ +140.1°, and **SR14**, mp 110–111 °C, $[\alpha]_D$ −127.3°. The former was in close agreement with the reported rotation ($[\alpha]_D$ +145.8°) and melting point (108–109 °C) of natural aristolactone.[12] A mixture of the (−)-enantiomer **SR14** with natural aristolactone showed mp 80–90 °C. Thus natural (+)-aristolactone must possess the 6*R*,7*S* configuration.

The 17-membered allylic propargylic ether **15** was prepared by us for our first studies on the [2,3] Wittig ring contraction in connection with synthetic work on cembranolides.[3a] It yielded a 70:30 mixture of the trans and cis alcohols **16** and **18** upon treatment with *n*-BuLi in THF at −78 °C. In the present study we treated ether **15** with lithiated **SS4** under various conditions. Our findings are summarized in Table III. In THF, reaction occurred at −55 to −10 °C and led to a separable 70:30 mixture of trans and cis alcohols **16** and **18**, each of which proved to be nearly racemic as judged by analysis of the $^1$H NMR spectrum of the *O*-methylmandelates **17** and **19**. Reaction in pentane was considerably slower and gave a 60:40 mixture of trans and cis products **16** and **18**. The trans product **16** was optically active, $[\alpha]_D$ +33.4°. Analysis via the (*S*)-*O*-methylmandelates **17** showed an ee of 33% and permitted assignment of the major isomer as *R,R* (see Figure 1).[10] The most satisfactory solvent examined was 9:1 pentane–THF. The rearrangement was complete within 2 h at −35 to 10 °C and afforded a 70:30 mixture of trans and cis products **16** and **18** in 78% yield. Interestingly the major trans product, $[\alpha]_D$ −31.0°, was found to be the *S,S* isomer **SS16**, the enantiomer of the product obtained by employing pentane alone as the solvent. Such solvent effects have been observed for other deprotonation reactions employing chiral amide bases.[7d] In ether, the rearrangement was rapid and efficient affording (−)-**SS16** as the major trans enantiomer, but in low ee. As expected, use of lithiated **RR4** as the chiral base in 9:1 pentane–THF yielded **RR16** as the major trans enantiomer with an ee comparable to that observed for **SS16** obtained with lithiated **SS4** under similar conditions.

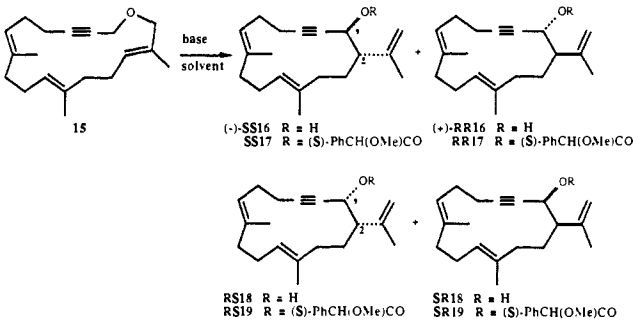
As the final phase in our initial studies, we examined the chiral base induced [2,3] Wittig rearrangement of the crotyl ethers **20a–c** (Table IV). These systems have previously been found to re-

(10) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Pontícello, G. S.; Vargas, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(11) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615. Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

(12) (a) Steele, J. W.; Stenlake, J. B.; Williams, W. D. *J. Chem. Soc.* **1959**, 3289. (b) Lange, G. *J. Chem. Res., Miniprint* **1982**, 3261.

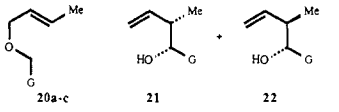
**Table III.** [2,3] Wittig Ring Contraction of Ether **15** with Lithium Bis(1-phenylethyl)amide Bases




| base | solvent | $T$, °C | $t$, h | yield, % | **16:18** | $[a]_D$,[a] deg | ee,[a,b] % |
|---|---|---|---|---|---|---|---|
| Li-**SS4** | THF | −55 to −10 | 1.5 | 56 | 70:30 | | <5 |
| | pentane | −10 to 20 | 10 | 23 | 60:40 | +33.4 | 33 |
| | pentane-THF (9:1) | −35 to 10 | 2 | 78 | 70:30 | −30.5 | 29 |
| | ether | −35 to −20 | 1.5 | 73 | 70:30 | −10.2 | 10 |
| Li-**RR4** | pentane-THF (9:1) | −40 to −5 | 2 | 73 | 70:30 | +25.1 | 23 |

[a] Values are for the trans isomer **16**. [b] Based on $^1$H NMR analysis of the (*S*)-*O*-methylmandelate.

**Table IV.** [2,3] Wittig Rearrangements of Acyclic Allylic Ethers with Li-**SS4** in THF[a]




| ether | G | T, °C | $t$, h | yield, % | **21:22**[b] | ee, % |
|---|---|---|---|---|---|---|
| **20a** | C≡CH | −78 to −20 | 4 | 50 | 2:98 | <5[c] |
| **20a** | C≡CH | −78 to −15 | 4 | 68[d] | 5:95 | 0[c] |
| **20a** | C≡CH | −78 to −20 | 10 | 70[e] | 2:98 | 0[f] |
| **20b** | $CO_2H$ | −78 to −50 | 4 | 85 | 90:10[g] | 0[f] |
| **20c** | $CON(CH_2)_4$ | −78 | 5 | 85 | 95:5 | 0[f] |

[a] Unless otherwise specified. [b] Stereochemistry is assigned by analogy with related rearrangements.[1] [c] Analysis via the (*S*)-*O*-methylmandelate. [d] The solvent was ether. [e] The solvent was 9:1 pentane–THF. [f] Based on optical rotation measurements. [g] Analysis via the methyl ester, G = $CO_2Me$.

arrange with high diastereoselectivity upon treatment with achiral bases.[1] We observed comparably high diastereoselectivity with lithio-**SS4**, but the products were racemic.

As stated in the introduction, a chiral base initiated [2,3] Wittig rearrangement leading to enantiomerically enriched products would require one or more of the following conditions to be met subsequent to chiral recognition: (1) concerted [2,3] rearrangement without prior formation of a free carbanion, (2) formation of a configurationally stable chiral (stereogenic)[13] organolithium intermediate,[14] (3) formation of an anion (chirotopic)[13] whose *si* or *re* orientation to the allylic ether double bond would be preserved because of a high steric barrier to jump-rope rotation,[8] (4) formation of a configurationlly stable chiral anion–conjugate acid pair. The observed increase in enantioselectivity with decreasing ring size and the lack of enantioselectivity in the acyclic propargylic ether rearrangements suggest that conditions 1 and 4 are not generally operative, but 3 and possibly 2 may be. Conceivably, condition 1 might be operational with the 13-membered ether **1** and, to a lesser degree, the 17-membered ether **15** where the reacting centers are held into close proximity by the relatively inflexible trans enyne or dienyne connecting chains. Ring size would also play an important role with regard to conditions 2 and 3 as the linear arrangement of an $sp^2$ propargylic anion imposes greater rigidity in the 13-membered ether, thereby inducing a higher racemization barrier. Such a barrier would be lower in the 17-membered ether and absent in the acyclic cases.

Possible transition states for these rearrangements are pictured in Figure 2. The assumption is made that the chiral amide base coordinates with a propargylic proton in the chairlike conformation

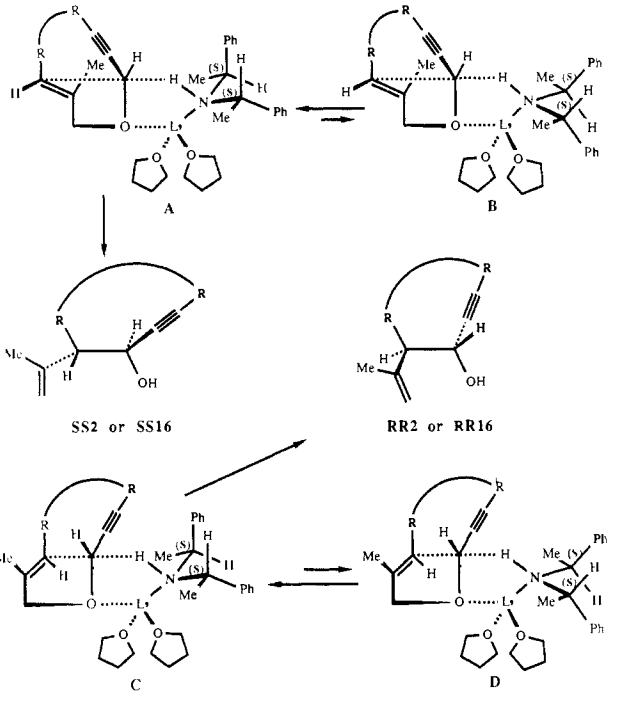



**Figure 2.** Transition states for [2,3] Wittig ring contractions promoted by Li-**SS4**.

illustrated.[15] Coordination of the lithium cation to the amide nitrogen, the ether oxygen, and the solvent leads to a rigid complex

(13) Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.
(14) α-Alkoxy*alkyl*lithium compounds have been shown to be configurationally stable. Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5422.

(15) This conformation was selected on the basis of calculations with W. C. Still's MacroModel program in which *anti*-2,4-diphenylpentane was used to approximate the tetracoordinated amine. We are grateful to Dr. Stephen L. Crooks for performing these calculations.

in which the "axial" phenyl grouping of the amide base essentially directs the stereochemistry of the deprotonation. Complexes B and D are disfavored by 1,3-interactions between an "axial" phenyl and coordinating solvent molecules (e.g., THF). In the absence of coordinating solvents, the lithium ion could associate with basic centers (N and O) in other substrate molecules. Complexes A and C are free of the 1,3-phenyl/solvent interactions. Complex A should be of lower energy as it lacks the unfavorable 1,4-phenyl/alkyne interaction present in complex C. Although this picture correlates the major findings of this study, it is undoubtedly an oversimplification as it ignores the important question of aggregation.[16]

Additional studies on chiral base initiated [2,3] Wittig rearrangements are in progress and will be described in due course.

## Experimental Section

**(−)-(*R*)-*N*-(1-Phenylethyl)-α-methylbenzylideneamine (R3).** The procedure of Overberger et al. was followed.[9] A solution of 12.7 g (0.100 mol) of (+)-(*R*)-1-phenylethylamine [Fluka, $[\alpha]_D$ +29.7° (*c* 10.85); (*S*)-*O*-methylmandelamide derivative, prepared according to Trost et al.,[10] mp 102 °C. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.84; H, 7.06; N, 5.20. Found: C, 75.75; H, 7.08; N, 5.16.] and freshly distilled acetophenone (12.0 g, 0.100 mol) in 120 mL of dry benzene containing a catalytic amount of *p*-toluenesulfonic acid was refluxed under nitrogen while water was continuously removed by means of a Dean–Stark trap. A total of 2.2 mL (0.12 mol) of water was collected overnight, whereupon the solvent was removed under reduced pressure and the residue was distilled to yield 14.5 g (65%) of colorless oil: bp 124 °C (0.05 mmHg); IR (film) $\nu$ 3070, 3050, 3010, 2960, 2910, 2880, 1630, 1600, 1570, 1480, 1440, 1360, 1270, 1260, 850, 690 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.55 (d, $J$ = 7 Hz, $CH_3CH$), 2.28 (s, vinyl $CH_3$), 4.85 (q, $J$ = 7 Hz, benzylic H), 7.1–7.9 (m, aromatic H); $[\alpha]_D$ −73.3° (*c* 2.14, $CHCl_3$) [reported for the *S* imine, $[\alpha]_D$ −97.6° (solvent and concentration unspecified)[9]]. Anal. Calcd for $C_{16}H_{17}N$: C, 86.10; H, 7.62; N, 6.28. Found: C, 86.00; H, 7.69; N, 6.22.

**(+)-Bis[(*R*)-1-phenylethyl]amine (RR4).** The procedure of Overberger et al. was followed.[9] A solution of 12.6 g (0.056 mol) of (−)(*R*)-*N*-(1-phenylethyl)-α-methylbenzylideneamine (**R3**) in 80 mL of THF containing 0.5 g of 10% palladium on carbon was shaken in a Paar hydrogenator for 2 h. After filtration of the catalyst, solvent was evaporated at reduced pressure, and the residue was distilled to yield 10 g (80%) of colorless oil, bp 98–104 °C (0.2 mmHg). The amine was converted to the hydrochloride salt and fractionally crystallized by slow addition to a stirred hot solution of 250 mL of water containing 8 mL of concentrated hydrochloric acid. After slow cooling, the salt was filtered and washed with cold water. The solid was then treated with a solution of KOH in water with stirring for 1 h, and the mixture was extracted twice with ether. The combined organic layers were washed with water and brine and were dried over anhydrous $MgSO_4$. Removal of solvent left an oil that was purified by distillation [bp 86–96 °C (0.05 mmHg)], yielding 6.1 g (61%) of the *R,R* amine **4**: IR (film) $\nu$ 3090, 3070, 3030, 2960, 2920, 2860, 1605, 1490, 1450, 1360, 1200, 1140, 1040, 750, 700 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.26 (d, $J$ = 6.5 Hz, $CH_3$), 1.56 (s, NH), 3.48 (q, $J$ = 7 Hz, $CH_3CH$), 7.1–7.4 (m, aromatic H); $[\alpha]_D$ +167.6° (*c* 1.1, $CHCl_3$) [reported for bis[(*S*)-1-phenylethyl]-amine $[\alpha]_D$ −196.3° (solvent and concentration unspecified)[9]]; $[\alpha]^{20}_D$ −139° (*c* 1.8, ethanol, corrected for 14% meso impurity).[7e] Anal. Calcd for $C_{16}H_{19}N$: C, 85.33; H, 8.44. Found: C, 85.26; H, 8.53.

The urea derivative **RRR5** was prepared by treating a solution of 204 mg (0.91 mmol) of the amine **RR4** in 2 mL of $CH_2Cl_2$ and 1 mL of pyridine with 0.5 mL (2.3 mmol) of (*R*)-1-(1-naphthyl)ethyl isocyanate. The solution was stirred for 2 days at room temperature, water was added, and the product was extracted with ether. The extracts were washed with 10% aqueous HCl and water and dried over $MgSO_4$. No amine was recovered upon base treatment of the acid wash. Filtration of the drying agent from the organic extracts and removal of solvent afforded an oil. The $^1H$ NMR spectrum of this material showed a set of $CH_3$ doublets at $\delta$ 1.06 (3 H, $J$ = 7 Hz) and 1.61 (6 H, $J$ = 7 Hz) characteristic of the *R,R,R* diastereoisomer (see below). Purification by chromatography on silica gel afforded the urea **RRR5** as a white solid: mp 163–165 °C; IR ($CCl_4$) $\nu$ 3420, 3070, 2980, 2940, 2880, 1645, 1600, 1510, 1455, 1410, 1380, 1245, 1210, 1170, 1090, 710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.06 (d, $J$ = 7 Hz, $CH_3CH$, 3 H), 1.61 (d, $J$ = 7 Hz, $CH_3CH$, 6 H), 4.25 (d, $J$ = 7 Hz, NH), 5.36 (q, $J$ = 7 Hz, $CH_3CH$, 2 H), 5.64 (q, $J$ = 7 Hz, $CH_3CH$, 1 H), 7.0–8.2 (m, aromatic H).

**(−)-Bis[(*S*)-1-phenylethyl]amine (SS4).** The procedure of Overberger et al.[9] was followed as described above for **R3** and **RR4** but with (−)-(*S*)-1-phenylethylamine as starting material [Fluka, $[\alpha]_D$ −29.8° (*c* 10.35); (*S*)-*O*-methylmandelamide derivative, prepared according to Trost et al.,[10] mp 114–115 °C. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.84; H, 7.06; N, 5.20. Found: C, 75.88; H, 7.14; N, 5.15.]. The derived imine **S3**, $[\alpha]_D$ +66.8° (*c* 6.35, $CHCl_3$) [reported $[\alpha]_D$ −97.6° (solvent and concentration unspecified)[9]], was hydrogenated as described above, affording the amine **SS4**, which was purified via the hydrochloride to give material with $[\alpha]_D$ −171.6° (*c* 6.71, $CHCl_3$) [reported $[\alpha]_D$ −196.3° (solvent and concentration unspecified)[9]].

The urea derivative **RSS5** was prepared according to the procedure described above. The crude product showed a set of $CH_3$ doublets at $\delta$ 1.42 (3 H, $J$ = 7 Hz) and 1.72 (6 H, $J$ = 7 Hz) characteristic of the **RSS** diastereoisomer (see above). Purification by chromatography on silica gel afforded the urea **RSS5** as a viscous oil: IR ($CCl_4$) $\nu$ 3420, 3080, 2980, 2940, 2880, 1640, 1600, 1500, 1450, 1405, 1380, 1310, 1240, 1210, 1170, 1090, 1060, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.42 (d, $J$ = 7 Hz, $CH_3CH$, 3 H), 1.72 (d, $J$ = 7 Hz, $CH_3CH$, 6 H), 4.46 (d, $J$ = 7 Hz, NH, 1 H), 5.36 (q, $J$ = 7 Hz, $CH_3CH$, 2 H), 5.70 (q, $J$ = 7 Hz, $CH_3CH$, 1 H), 6.4–8.0 (m, aromatic H).

**[2,3] Wittig Ring Contraction of Ether 1. A. Through Use of the *S,S* Base.** The chiral amide base was formed from 910 mg (7.5 mmol) of (*S,S*)-bis(1-phenylethyl)amine (**SS4**) in 10 mL of THF at 0 °C under a nitrogen atmosphere by dropwise addition of 2.7 mL (6.8 mmol) of 2.5 *M* *n*-butyllithium in hexane. After 30 min at 0 °C, the solution of amide was slowly added via cannula to a stirred, cooled (−41 °C) solution of 438 mg (2.15 mmol) of cyclic ether **1** in 10 mL of THF. The resulting mixture and the bath were allowed to warm slowly for 20 min to −30 °C, water was added, and the mixture was diluted with ether. The separated aqueous layer was extracted with ether. The combined ether layers were washed with 5% aqueous HCl, water, and brine and dried over anhydrous $MgSO_4$. Filtration and removal of solvent gave an oil that was purified by column chromatography on silica gel (15% ethyl acetate–hexanes) to give 303 mg (70%) of the (−)-propargylic alcohol **SS2**: IR (film) $\nu$ 3450, 3050, 2900, 2895, 2250, 2200, 1640, 1440, 1025, 880 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.4–2.4 (m, $CH_2$s), 1.68 (s, vinyl $CH_3$s), 4.05 (m, carbinyl H), 4.80 (s, vinyl Hs, 2 H), 5.08 (s, vinyl H); $[\alpha]_D$ −27.1° (*c* 5.4, $CHCl_3$; ee = 57%). Material of 60–80% ee was obtained in 70–85% yield from rearrangements conducted under comparable conditions to those described above.

**B. Through Use of the *R,R* Base.** The procedure described above was followed with 5.3 mmol of (*R,R*)-bis(1-phenylethyl)amine (**RR4**) in 10 mL of THF and 4.5 mmol of 2.5 M *n*-butyllithium. The resulting mixture was added to a cooled solution (−78 °C) of 310 mg (1.5 mmol) of cyclic ether **1** in 5 mL of THF. After 3 h, the reaction was quenched at −30 °C with water to afford, after workup and purification, 228 mg (73%) of (+)-propargylic alcohol **RR2** with spectral properties identical with those of a sample above, $[\alpha]_D$ +29.1° (*c* 3.67, $CHCl_3$; ee ≈ 61%). Material of 60–75% ee was obtained in 70–85% yield from rearrangements conducted under comparable conditions to those described above.

**(1*R*,2*R*)-(5*E*)-2-Isopropenyl-5-methyl-5-cyclodecen-9-ynyl (*S*)-*O*-Methylmandelate (RR6).** To a solution of 330 mg (1.6 mmol) of (+)-propargylic alcohol **RR2** [$[\alpha]_D$ +33.4 (*c* 4.2, $CHCl_3$; ee = 70%)], 320 mg (1.9 mmol) of (*S*)-*O*-methyl mandelic acid, and 450 mg (2.2 mmol) of DCC in 7 mL of $CH_2Cl_2$ was added a catalytic amount of DMAP.[10] After being stirred overnight at room temperature under nitrogen, the mixture was concentrated under reduced pressure to afford a yellow solid. This solid was washed with ether and filtered, and the organic layer was concentrated to afford a white viscous oil that was chromatographed on silica gel (2% ethyl acetate–hexanes), yielding 322 mg (71%) of the (*S*)-*O*-methylmandelic ester **RR6** as a colorless viscous oil (greater than 90% pure by $^1H$ NMR analysis): IR (film) $\nu$ 3060, 3020, 2920, 2850, 2220, 2110, 1745, 1640, 1485, 1445, 1140, 1110, 990, 749, 690 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.09 (s, $CH_3$), 1.4–2.4 (m, $CH_2$), 2.33 (s, vinyl $CH_3$), 2.46 (dt, $J$ = 11, 4 Hz, H2), 3.38 (s, $CH_3O$), 4.25 [(s, $CH$(OMe)], 4.48 (s, vinyl H), 4.62 (s, vinyl H), 5.95–6.2 (m, carbinyl and vinyl H), 7.2–7.5 (m, aromatic H); MS, *m/e* 203 (M − *O*-methylmandelate).

**(+)-(1*R*,2*R*)-(5*E*)-2-Isopropenyl-5-methyl-5-cyclodecen-9-yn-1-ol (RR2).** A solution of 216 mg (0.61 mmol) of purified (*S*)-*O*-methylmandelate **RR6** was stirred at room temperature with 11 mL of 1 M KOH in MeOH. After 45 min, saturated aqueous NaCl and ether were added, the layers were separated, and the aqueous layer was extracted with ether. The extracts were combined, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography on silica gel (15% ethyl acetate–hexanes) yielded 86 mg (70%) of the pure (+)-alcohol **RR2** with spectral properties identical with those of the

(16) Cf. Seebach, D. *Proceedings of the Robert A. Welch Foundation Conference on Chemical Research XXVII; Stereospecificity in Chemistry and Biochemistry*; Houston, TX, 1983.

sample prepared above: $[\alpha]_D$ +47.1° (*c* 4.3, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.20; H, 9.90.

**(1*S*,2*S*)-(5*E*)-2-Isopropenyl-5-methyl-5-cyclodecen-9-ynyl (*S*)-*O*-Methylmandelate (SS6).** The procedure described for **RR6** was followed with 326 mg (1.60 mmol) of (−)-propargylic alcohol **SS2** [$[\alpha]_D$ −36.5° (*c* 4.94, $CHCl_3$; ee = 77%)], 0.5 g (3 mmol) of (*S*)-*O*-methylmandelic acid, 0.4 g (2.0 mmol) of DCC, and a catalytic amount of DMAP in 12 mL of $CH_2Cl_2$. The mixture was stirred overnight, and the product was isolated by removal of solvent and chromatography on silica gel (2% ethyl acetate/hexanes) to give 360 mg (73%) of (*S*)-*O*-methylmandelate **SS6** (greater than 95% pure by $^1H$ NMR analysis) as a colorless viscous oil: IR (film) $\nu$ 3070, 3030, 2920, 2860, 2820, 2250, 2220, 1750, 1640, 1490, 1450, 1380, 1190, 1100, 980, 920, 730, 700 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.43 (s, $CH_3$), 1.6–2.4 (m, $CH_2$), 2.26 (s, vinyl $CH_3$), 2.58 (dt, $J$ = 11, 4 Hz, H2), 3.38 (s, $CH_3O$), 4.58 [(s, C*H*(OMe)], 4.70 (m, vinyl H, 2 H), 5.28 (s, vinyl H), 7.2–7.5 (m, aromatic H); MS, *m/e* 203 (M − *O*-methylmandelate).

**(−)-(1*S*,2*S*)-(5*E*)-2-Isopropenyl-5-methyl-5-cyclodecen-9-yn-1-ol (SS2).** The procedure described for **RR2** was followed with 360 mg (1.03 mmol) of purified (*S*)-*O*-methylmandelate **SS6** and 10 mL of 1 M KOH in MeOH. After 1 h at room temperature, the product was isolated as described, giving 196 mg (96%) of (−)-propargylic alcohol **SS2** as a colorless oil with spectral properties identical with those of a sample above: $[\alpha]_D$ −47.4° (*c* 3.45, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.30; H, 9.88.

**(+)-(1*R*,2*S*)-(5*E*)-2-Isopropenyl-5-methyl-5-cyclodecen-9-yn-1-ol (RS10).** To a solution of 230 mg (1.13 mmol) of purified (−)-propargylic alcohol **SS2**, $[\alpha]_D$ −47.4° (*c* 4.87, $CHCl_3$), and 0.8 g (3.1 mmol) of triphenylphosphine in 5 mL of dry benzene was added over 5 h at room temperature a solution of 0.5 g (2.40 mmol) of DEAD and 0.35 g (2.85 mmol) of benzoic acid in 8 mL of dry benzene. After 8 h, the reaction mixture was concentrated and stirred at room temperature with 10 mL of 1 M KOH in MeOH for 40 min. After workup by ether extraction and purification by column chromatography on silica gel, 179 mg (78%) of (+) alcohol **RS10** was isolated as a colorless oil: $[\alpha]_D$ +47.4° (*c*, 4.04, $CHCl_3$); IR (film) $\nu$ 3450, 3030, 2950, 2900, 2230, 2200, 1640, 1440, 1380, 900 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.6–2.5 (m, $CH_2$), 1.69 (s, vinyl $CH_3$), 1.79 (s, vinyl $CH_3$), 4.3 (s, carbinyl H), 4.9 (s, vinyl H, 2 H), 5.1 (s, vinyl H). Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.33; H, 9.90.

**(−)-(1*S*,2*R*)-(5*E*)-2-Isopropenyl-5-methyl-5-cyclodecen-9-yn-1-ol (SR10).** The procedure described for **RS10** was followed. To a solution of 86 mg (0.42 mmol) of purified (+)-propargylic alcohol **RR2** [$[\alpha]_D$ +47.1 (*c* 4.3, $CHCl_3$); ee >90%] and 300 mg (1.14 mmol) of triphenylphosphine in 4 mL of dry benzene was added over 4 h at room temperature a solution of 210 mg (1.15 mmol) of DEAD and 130 mg (1.07 mmol) of benzoic acid in 5 mL of dry benzene. After 8 h, the reaction mixture was concentrated and stirred at room temperature with 4 mL of 1 M KOH in MeOH for 1.5 h. After workup and purification, 55 mg (64%) of (−) alcohol **SR10** was isolated as a colorless oil, $[\alpha]_D$ −43.9° (*c* 2.25, $CHCl_3$). The spectral properties of this material were identical with those of a sample of the (+) antipode **RS10** prepared above. Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.26; H, 9.83.

**(6*R*,7*S*)-(4*Z*,10*E*)-6-Hydroxy-7-isopropenyl-10-methyl-4,10-cyclodecadiene-4-carboxylic Acid Lactone. (+)-Aristolactone (RS14).** To a stirred solution of 150 mg (0.735 mmol) of the foregoing (+)-propargylic alcohol **RS10**, $[\alpha]_D$ +47.4° (*c* 4.04, $CHCl_3$), in 5.6 mL of THF was added 0.35 mL (1.19 mmol) of 3.4 M Red-Al.[11] After 2 days at room temperature (TLC analysis of the reaction mixture showed some starting material), 300 mg (1.3 mmol) of *N*-iodosuccinimide in 3 mL of THF was added, and workup was carried out by ether extraction. The combined dried extracts were concentrated to ca. 5 mL at reduced pressure, affording a solution of vinyl iodide **RS12** in THF. To this solution were added 50 mg (0.07 mmol) of $(Ph_3P)_2PdCl_2$, 140 mg (1.0 mmol) of anhydrous $K_2CO_3$, and 2 drops of anhydrous hydrazine. The mixture was placed in a steel bomb under 80 psi of CO for 14 h at 35 °C. Extraction with ether and preparative layer chromatography gave 16 mg (10%) of (+)-aristolactone (**RS14**): mp 110–111 °C (pentane) [mmp with natural (+)-aristolactone 108–109 °C]; IR (KBr) $\nu$ 3090, 2980, 2930, 1735, 1640, 1430, 1375, 1205, 1060, 900 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.47 (s, C10 vinyl $CH_3$), 1.50–1.70 (m), 1.80 (s, isopropenyl $CH_3$), 1.85–2.65 (m, allylic $CH_2$), 2.74 (dd, $J$ = 12, 7 Hz, H2$\beta$), 4.57 (d, $J$ = 12 Hz, H1), 4.64 (s, isopropenyl vinyl H), 4.81 (s, isopropenyl vinyl H), 4.97 (s, carbinyl H), 6.65 (s, H5); $[\alpha]_D$ +140.1° (*c* 0.91, $CHCl_3$; ee ~ 96%) [reported for natural (+)-aristolactone $[\alpha]_D$ +145.8° (*c* 0.73, $CHCl_3$); mp 108–109 °C]. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.59; H, 8.62. Found: C, 77.69; H, 8.70.

**(6*S*,7*R*)-(4*Z*,10*E*)-6-Hydroxy-7-isopropenyl-10-methyl-4,10-cyclodecadiene-4-carboxylic Acid Lactone. (−)-Aristolactone (SR14).** The procedure described for **RS14** was followed with 45 mg (0.22 mmol) of the foregoing (−)-propargylic alcohol **SR10**, $[\alpha]_D$ −43.9° (*c* 2.25, $CHCl_3$; ee ~ 90%), in 1.5 mL of THF and 0.11 mL (1.19 mmol) of 3.4 M Red-Al. Following quench with 70 mg (0.31 mmol) of *N*-iodosuccinimide in 2 mL of THF and workup, a solution of vinyl iodide **SR12** in THF was obtained. To this solution were added 30 mg (0.05 mmol) of $(Ph_3P)_2PdCl_2$, 50 mg (0.36 mmol) of $K_2CO_3$, and 2 drops of anhydrous hydrazine. After 10 h under 80 psi of CO at 35 °C, 12 mg (24%) of (−)-aristolactone (**SR14**), mp 110–111 °C (mmp with authentic (+)-aristolactone 80–90 °C), was obtained, $[\alpha]_D$ −127.3° (*c* 0.6, $CHCl_3$; ee ~ 87%), whose spectral properties were identical with those reported above. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.59; H, 8.62. Found: C, 77.44; H, 8.71.

**Typical Procedure for [2,3] Wittig Ring Contraction of Ether 15.** The chiral amide base was formed from 0.35 g (1.60 mmol) of (*S*,*S*)-bis(1-phenylethyl)amine (**SS4**) in a mixture of 7 mL of pentane and 0.6 mL of THF at 0 °C under a nitrogen atmosphere by dropwise addition of 0.7 mL (1.61 mmol) of 2.5 M *n*-butyllithium in hexane. After 30 min at 0 °C, the solution of amide was slowly added via cannula to a stirred, cooled (−40 °C) solution of 103 mg (0.38 mmol) of cyclic ether **15** in a mixture of 7 mL of pentane and 0.6 mL of THF. The bath was allowed to warm slowly over 2.5 h to −5 °C, the reaction was quenched with water, and the mixture was extracted with ether. The combined extracts were washed with 5% aqueous HCl, water, and brine and dried over anhydrous $MgSO_4$. Filtration and removal of solvent gave an oil that was purified by column chromatography on silica gel (10% ethyl acetate–hexanes) to give 23 mg (21%) of the cis propargylic alcohol **18**: IR ($CCl_4$) $\nu$ 3610, 3070, 2980, 2960, 2920, 2860, 1660, 1450, 1430, 1380, 1030, 960, 850, 730 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.56, 1.57, 1.77 (s, vinyl $CH_3$), 1.50–2.5 (m, allylic $CH_2$), 4.47 (br s, carbinyl H), 4.84, 4.96 (s, vinyl H, 2 H), 5.1–5.2 (m, vinyl H, 2 H); $[\alpha]_D$ −3.1° (*c* 1.14, $CHCl_3$). The spectral properties were identical with those of the racemic material.[3a]

Continued elution afforded 48 mg (45%) of the trans propargylic alcohol **16**: IR ($CCl_4$) $\nu$ 3710, 3650, 3080, 2980, 2930, 2860, 1645, 1445, 1435, 1380, 1140, 1065, 1035, 910, 735 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.58 (s, vinyl $CH_3$, 6 H), 1.62 (s, vinyl $CH_3$), 1.3–2.6 (m, allylic $CH_2$), 4.05 (d, $J$ = 10 Hz, carbinyl H), 4.82, 4.98 (s, vinyl H, 2 H), 5.15–5.25 (m, vinyl, 2 H); $[\alpha]_D$ −31.0° (*c* 2.4, $CHCl_3$; ee = 30%, see below). The spectral properties were identical with those of the racemic material.[3a]

**(1*R*,2*R*)-(5*E*,9*E*)-2-Isopropenyl-5,9-dimethyl-5,9-cyclotetradecadien-13-ynyl (*S*)-*O*-Methylmandelate (17).** A solution of 35 mg (0.13 mmol) of alcohol **16** ($[\alpha]_D$ −31°), excess DCC and (*S*)-*O*-methylmandelic acid, and a catalytic amount of DMAP in 2.5 mL of $CH_2Cl_2$ was stirred for 12 h at room temperature.[10] The solvent was removed under reduced pressure, and the resulting crude mixture was purified by silica gel chromatography (2% ethyl acetate–hexanes), affording the mandelate **17** as a clear oil: IR (film $CCl_4$) $\nu$ 3080, 3040, 2930, 2860, 2240, 1750, 1450, 1220, 1170, 1115, 1000, 910, 730, 700 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.15 (s, isopropenyl $CH_3$ of minor diastereomer), 1.45 (s, isopropenyl $CH_3$ of major diastereomer), 1.54, 1.62 (vinyl $CH_3$), 2.44 (dt, $J$ = 1.5, 12.5 Hz, H1 of minor diastereomer), 2.55 (dt, $J$ = 1.5, 12.5 Hz, H1 of major diastereomer), 3.30 (s, MeO of major diastereomer), 3.35 (s, MeO of minor diastereomer), 4.39 (q, $J$ = 1.7 Hz, isopropenyl H of major diastereomer), 4.41 (s, C*H*OMe of major diastereomer), 4.70 (s, C*H*OMe of minor diastereomer), 4.71 (s, isopropenyl H), 4.75 (t, $J$ = 1.7 Hz, isopropenyl H of minor diastereomer), 5.0–5.2 (m, vinyl H), 5.24 (dt, $J$ = 12.5, 1.0 Hz, H2 of major diastereomer), 7.1–7.5 (m, aromatic H). A diastereomeric ratio of ~2:1 could be estimated by integration of the appropriate signals: MS, *m/e* 420 (M + 1), 388 (M − MeO), 358 (M − 2Me − MeO), 299 (M − PhCH(OMe), 271 (M − PhCH(OMe)CO).

***rel*-(1*S*,2*R*)-(5*E*,9*E*)-2-Isopropenyl-5,9-dimethyl-5,9-cyclotetradecadien-13-ynyl (*S*)-*O*-Methylmandelate (19).** The procedure described above was followed with 19 mg (0.07 mmol) of propargylic alcohol **18** to give the (*S*)-*O*-methylmandelate **19** as a colorless viscous oil: IR (film $CCl_4$) $\nu$ 2960, 2940, 2860, 1740, 1460, 1355, 1230, 1110, 1070, 1020, 840 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.1–2.6 (m, vinyl $CH_3$, allylic $CH_2$), 3.37 and 3.40 (s, MeO), 4.18 (s, CHOMe), 4.44 (t, $J$ = 1.7 Hz, carbinyl H), 4.65 (s, CHOMe), 4.72 (s, vinyl H), 4.77 (t, $J$ = 1.7 Hz, carbinyl H), 5.0–5.2 (m, vinyl H, 2 H), 5.48 (s, isopropenyl H, 1 H), 7.2–7.5 (m, aromatic H). A diastereomeric ratio of ~1:1 could be estimated by integration of the appropriate signals. MS, *m/e* 420 (M + 1), 388 (M − MeO), 358 (M − 2Me − MeO), 299 (M − PhCH(OMe)), 271 (M − PhCH(OMe)CO).

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**Supplementary Material Available:** Experimental data for II, III, **RS7**, **RS8**, **S11**, and **21** and NMR spectra for **RRR5**, **RSS5**, **SS6**, **RR6**, **S11**, racemic 11, **SS17**, and **RR17** (11 pages). Ordering information is given on any current masthead page.

# A Novel Strategy for the Stereoselective Total Synthesis of C-17 Spiro Steroids. Total Synthesis of 19-Norcanrenone, a Formal Total Synthesis of 19-Norspironolactone

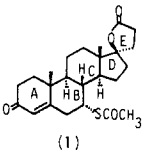
**Hideo Nemoto,[†] Shigekazu Fujita,[†] Mitsuo Nagai,[†] Keiichiro Fukumoto,*[†] and Tetsuji Kametani[‡]**

*Contribution from Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan, and Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan.* *Received September 25, 1987*

**Abstract:** The intramolecular (4 + 2) cycloaddition reactions of olefinic *o*-quinodimethanes, generated in situ by the thermolysis of olefinic benzocyclobutenes, lead stereoselectively to A-nor B-aromatic C-17 spiro steroids. This is a new and general methodology for the stereoselective synthesis of biologically important C-17 spiro steroids. This method yields the total synthesis of 19-norcanrenone, constituting a formal total synthesis of 19-norspironolactone.

Herein, we provide full details for the highly efficient stereocontrolled approach to steroids that have an unsymmetrically substituted spiro ring at C-17 position via intramolecular (4 + 2) cycloaddition reaction as a key stereodirecting process. This leads to a total synthesis of 19-norcanrenone.

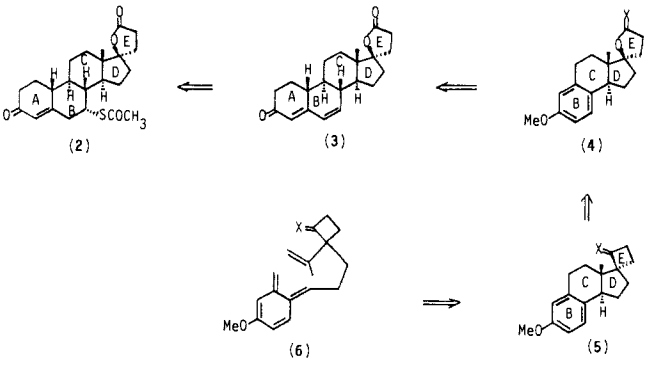
Since the first reports[1] on the synthesis and the antialdosterone activity of the steroidal spironolactone in the late 1950s, numerous efforts have been devoted[2] to the study of structurally diverse steroids, mainly because of the clinical importance of this type of steroids for the treatment of primary hyperaldosteronism, diseases related to secondary hyperaldosteronism (edema), and hypertension. Correlations of biological activity with variations in the structure of the spiro ring have indicated that the oxygen atom should be $\beta$ oriented[2a] and that substituent rings with more than five members display decreased activity.[2c,e] Of these reported, spironolactone (**1**) has emerged as the most effective representative that is capable of eliciting this type of biological response and that has been to date the only orally active aldosterone antagonist on the market since its discovery.



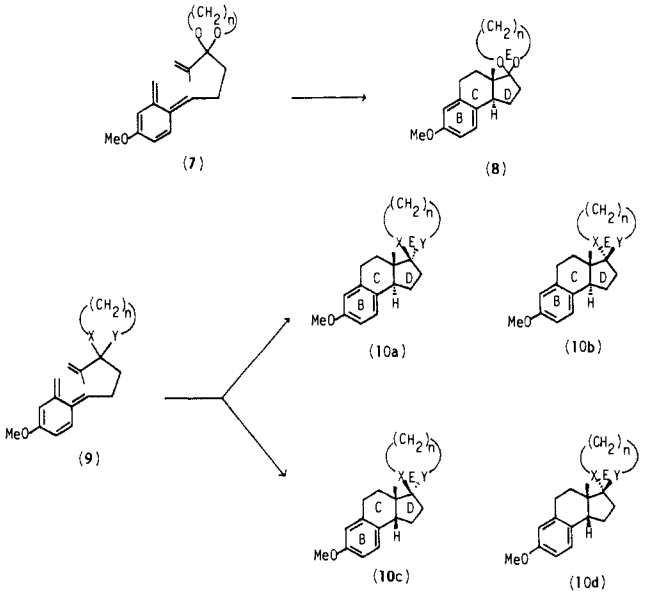
(1)

These facts and the distinctive structural feature—spirolactone group at C-17 and thioacetyl group at C-7 positions—have stimulated us to explore an effective methodology for the synthesis of 19-norspironolactone (**2**), which is more difficult to prepare and is expected to be more effective than its normal analogue **1**.[2m] Our synthetic strategy for this unique steroid **2** is characterized by the one-step creation of B, C, D, and E rings (**5**) in a stereoselective manner (Scheme I). Namely, stereoselective introduction of three successive chiral centers, $C_{13}$, $C_{14}$, and $C_{17}$ (steroid numbering), is achieved by using an intramolecular (4 + 2) cycloaddition reaction of the olefinic *o*-quinodimethane **6** as the key step and then the E-ring transformation (**5** → **4**) and functionalization at C-7 position, followed by A-ring formation (**4** → **3**). Conceptually this strategy contrasts to the traditional methods[2]

**Scheme I**



**Scheme II**



[†] Tohoku University.
[‡] Hoshi University.

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