6 H), [6] 2.08 (m, 1 H), [11] 1.91 (d, J = 1.3 Hz, 3 H), [4] 1.88 (dt, J = 10, 2.3 Hz, 1 H), [9] 1.43–1.52 (m, 2 H), [12] 1.00 (s, 3 H); IR (neat) 3000, 2940, 1710, 1670, 1480, 1415, 1360, 1290, 1080, 1060, 1025 cm^{-1}.

Acknowledgment. We wish to express thanks to Drs. H. M. Bell and H. C. Dorn for valuable discussions of rather complex NMR spectra and to Messrs. G. Iannaccone and W. R. Bebout for recording the spectra. We also recognize partial support from the Department of Energy through a Reactor Sharing Grant at the Univesity of Missouri Research Reactor.

Registry No. 1, 111349-98-5; 2, 111349-99-6; VIII (original), 111350-06-2; X (original), 111350-05-1; X (revised), 111350-15-3; XI (original), 111350-00-6; XI (revised), 111350-12-0; XIV (original), 111350-03-9; XV (original), 111350-01-7; XV (revised), 111350-13-1; XVI (original), 111350-04-0; XVI (revised), 111350-14-2; XVII (original), 111350-07-3; XVIII (original), 111350-08-4; XIX (original), 111350-10-8; XX (original), 111350-09-5; XX (revised), 111350-17-5; XXI (original), 111378-85-9; XXI (revised), 111350-16-4; 1,2,3,6-tetrahydro-3-methyl-3-(1,2-dimethyl-3-oxo-1-butenyl)pyridine, 111350-02-8; 1,2,3,6-tetrahydro-3-methyl-3-(1,2-dimethyl-3-oxobutyl)pyridine, 111350-11-9.

Supplementary Material Available: Tables II–V and Figures 1 and 2, showing details of X-ray crystallography, for $C_{12}H_{17}NO$ (6 pages). Ordering information is given on any current masthead page.

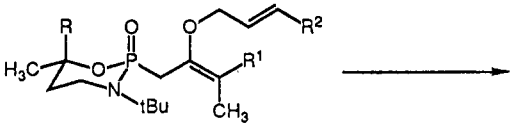
Communications

Carbanion-Accelerated Claisen Rearrangements. 4. Asymmetric Induction via 1,3,2-Oxazaphosphorinanes[1a]

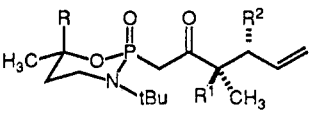
Summary: The anions dervied from allyl vinyl ethers **1** and **2** undergo rapid and highly selective Claisen rearrangements. The degree of asymmetric induction has been found to be uniformly high (ca. 90:10) for various substituent patterns but depends markedly on the presence of lithium cations. The absolute sense of asymmetric induction has been established using chiral, nonracemic 1,3,2-oxazaphosphorinane **2**. Two proposals for the transition structures of the phosphorus-stabilized anions are discussed.

Sir: Previous reports from these laboratories have established the accelerating effect of carbanionic functions in the Claisen rearrangement. Both sulfur-[2] and phosphorus-based[3] anion stabilizing groups have been shown to bring about enhancements in rate (>300-fold[4]) and internal stereoselectivity.[2c] One of the unique aspects of this carbanion-accelerated Claisen rearrangement (CACR) is the potential for asymmetric induction via chiral, anion-stabilizing groups. In particular, the phosphorus-based groups offer the advantage that their chirality may be auxiliary-derived by using readily available, recoverable diamines and amino alcohols, thus obviating the need for asymmetric synthesis at the heteroatom.[5,6] In this study we report that cyclic phosphoramidates **1** and **2** (Scheme I) rearrange anionically under mild conditions in good yields with significant levels of diastereoface selectivity. We also report herein the absolute stereochemical course of the rearrangements.

Scheme I



R = CH_3: **1**
R = H: **2**



R = CH_3: **3**
R = H: **4**

The amino alcohols **6**[7] and (*S*)-**8**[7] used in this study to create the chiral auxiliaries were easily prepared in large quantities as shown in Scheme II. (*S*)-Ethyl 3-hydroxybutanoate was obtained by yeast reduction[8] in excellent enantiomeric purity.[9a] The crystalline *tert*-butylamide (*S*)-**7**,[7,9b] prepared by the method of Weinreb,[10] was reduced with BH_3·THF to the requisite, chiral amino alcohol

(1) (a) Presented at the 193rd National Meeting of the American Chemical Society, Denver, CO, 1987; ORGN 228. (b) NSF Presidential Young Investigator 1985–1990. A. P. Sloan Fellow 1985–1987.

(2) (a) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (b) Denmark, S. E.; Harmata, M. A. *Tetrahedron Lett.* **1984**, *25*, 1543. (c) Denmark, S. E.; Harmata, M. A. *J. Org. Chem.* **1983**, *48*, 3369. (d) Harmata, M. A. Ph.D. Thesis, University of Illinois, Urbana, 1985. (e) Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Org. Chem.* **1987**, *52*, 4031.

(3) Denmark, S. E.; Marlin, J. E.; Dorow, R. L. "Abstracts of Papers", 191st National Meeting of the American Chemical Society, New York, April 1986; American Chemical Society: Washington, DC, 1986; ORGN 273.

(4) Leung, T. K., M. S. Thesis, University of Illinois, Urbana, 1985.

(5) For recent examples of this concept, see: (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754. (b) Hua, D. H.; Chan-Yu-King, R.; McKie, J. A.; Myer, L. *Ibid.* **1987**, *109*, 5026.

(6) Auxiliary-based asymmetric induction in the Claisen rearrangement has been demonstrated. (a) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443. (b) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1986**, *51*, 1377. (c) Kallmerten, J.; Gould, T. J. *Ibid.* **1986**, *51* 1152.

(7) All new compounds have been fully characterized by ^1H, ^{13}C, and ^{31}P NMR, IR, mass spectrometry and combustion analysis (±0.4%). Nondistillable phosphorus compounds have been identified by high-resolution MS.

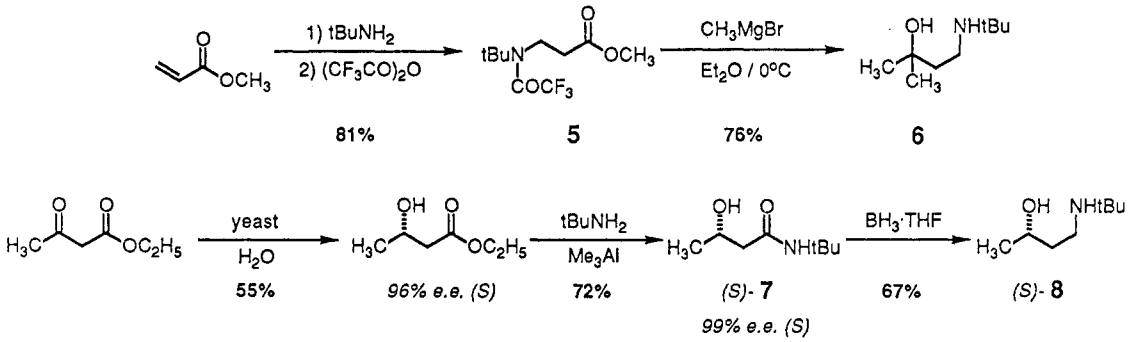
(8) (a) Seebach, D.; Sutter, M. A.; Weber, R. H.; Zuger, M. F. *Org. Synth.* **1984**, *63*, 1. (b) Ehrler, J.; Giovannini, F.; Lamatsch, B.; Seebach, D. *Chimia* **1986**, *40*, 172.

(9) (a) The enantiomeric excess of the 3-hydroxybutanoate was determined by using both optical rotation and Mosher analytical methods. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Enantiomeric excess established by the method of Pirkle. Pirkle, W. H.; Mahler, G.; Hyun, M. H. *J. Liquid Chromatogr.* **1986**, *9*, 443.

(10) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

0022-3263/87/1952-5742$01.50/0

Scheme II



Scheme III

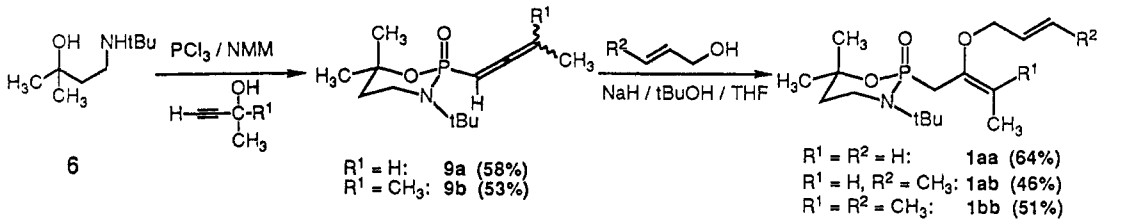


Table I. Carbanionic Claisen Rearrangement of 1[a]

entry	substr	product	base[b]	temp (°C)	yield (%)[c]	asym inductn[d] rel	asym inductn[d] internal
1	**1aa**	**3aa**	KDMSO	20	77	52:48	
2	**1aa**	**3aa**	KDMSO/LiCl[e]	20	81	91:9	
3	**1aa**	**3aa**	none	100	90	58:42	
4	**1ab**	**3ab**	KDMSO/LiCl[e]	20	80	92:8	98:2
5	**1ab**	**3ab**	none	100	84	58:42	77:23
6	**1bb**	**3bb**	KDMSO/LiCl[e]	20	94	92:8	
7	**1bb**	**3bb**	none	100	66	68:32	

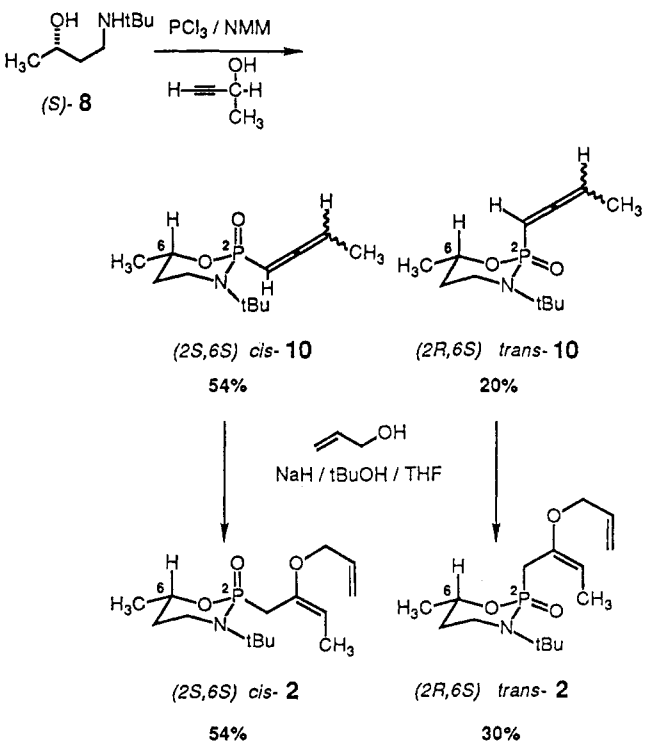
[a] All anionic rearrangements were done in 3/1 DMSO/THF (15 min), thermal rearrangements were done in THF (240 min). [b] 2–2.5 equiv of freshly prepared (KH/DMSO) base were used. [c] Yields after chromatography. [d] See text for definition. [e] Six equivalents of LiCl were added to the base before addition of 1.

(*S*)-**8**. The synthesis of **6** occasions no special comment.

The rearrangement substrate **1**[7] was prepared by combining **6** with PCl_3, *N*-methylmorpholine (NMM), and a propargyl alcohol to afford the allenyl phosphoramidates[11] **9a**[7] and **9b**,[7] Scheme III. Addition of various allyloxides to **9a** and **9b** completed the synthesis. In an analogous fashion (*S*)-**8** was transformed into a chromatographically resolvable mixture of isomers, epimeric at phosphorus. Each diastereomer was separately treated with sodium allyloxide to afford the epimeric rearrangement substrates, *cis*-**2**[7] and *trans*-**2**[7] (Scheme IV).[12]

The results of CACR with **1** are collected in Table I. The *relative* asymmetric induction is defined as the ability of the chiral phosphorus subunit to influence the creation of the new stereogenic centers in the rearrangement. The extent of chair/boat conformational selectivity is the *internal* asymmetric induction.[13] Several trends are noteworthy. First, all of the anionic rearrangements are significantly accelerated compared to the thermal processes (compare entries 2, 4, and 6 with 3, 5, and 7). Second, the relative asymmetric induction in the CACR is uniformly high (ca. 92:8) while the thermal rearrangements are poorly selective.[14] Third, the internal asymmetric induction in substrate **1ab** is excellent for the formation of the *syn*-dimethyl diastereomer **3ab**[7,15] in the anionic process.

Scheme IV



(11) Mark, V. In "Mechanisms of Molecular Migrations"; Thyagarajan, B. S., Ed.; Wiley: New York, 1969; Vol. 2, pp 319–437.

(12) The configuration at phosphorus in both *trans*-**2** and *cis*-**2** was established by X-ray crystallography. For a related case, see: Goodridge, R. J.; Hambley, T. W.; Ridley, D. D. *Aust. J. Chem.* **1986**, *39*, 591.

(13) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

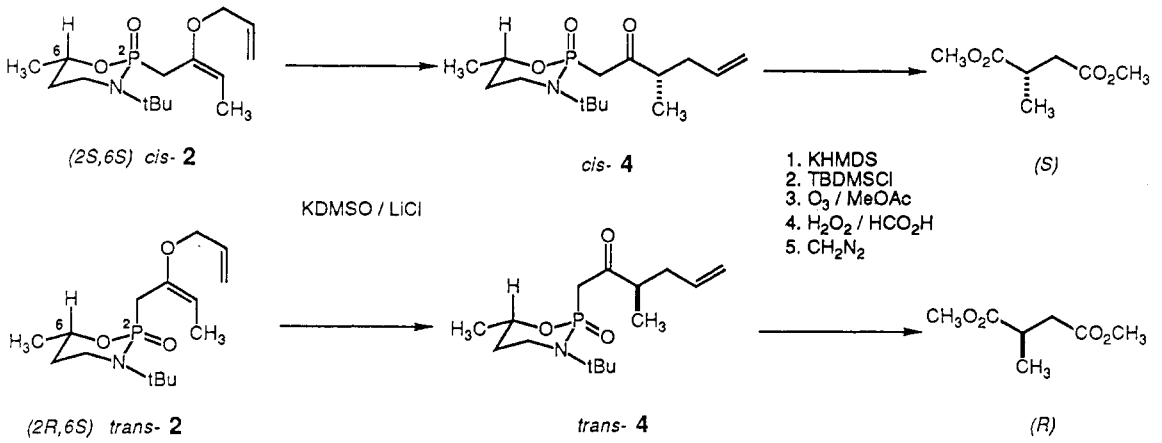
(14) The isomer ratios in **3aa** and **3ab** were determined by ^{31}P NMR of purified products. The isomer ratios in **3bb** and *cis*- and *trans*-**4** were determined by 500-MHz ^1H NMR.

Table II. Carbanionic Claisen Rearrangement of 2[a]

entry	substr	product	base[b]	LiCl (equiv)[c]	temp (°C)	yield (%)[d]	rel asym inductn[e]
1	*cis*-2	*cis*-4	KDMSO	0	20	62	50:50
2	*cis*-2	*cis*-4	KDMSO	1	20	77	65:35
3	*cis*-2	*cis*-4	KDMSO	2	20	69	80:20
4	*cis*-2	*cis*-4	KDMSO	6	20	78	90:10
5	*cis*-2	*cis*-4	KDMSO	12	20	65	89:11
6	*cis*-2	*cis*-4	LiDMSO[f]	0	20	65	90:10
7	*cis*-2	*cis*-4	none	0	100	93	66:34
8	*cis*-2	*cis*-4	none	6	100	90	64:36
9	*trans*-2	*trans*-4	KDMSO	6	20	71	8:92[g]

[a] All anionic rearrangements (15 min) were done in 3/1 DMSO/THF except entry 6 which was done in 2/1 THF/DMSO, thermal rearrangements (240 min) were done in THF. [b] 2–2.5 equiv of freshly prepared base were used. [c] LiCl was added to KDMSO before addition of ketone 2. [d] Yield after chromatography. [e] See text for definition. [f] Prepared from *n*-BuLi. [g] Opposite configuration in excess. See text for explanation.

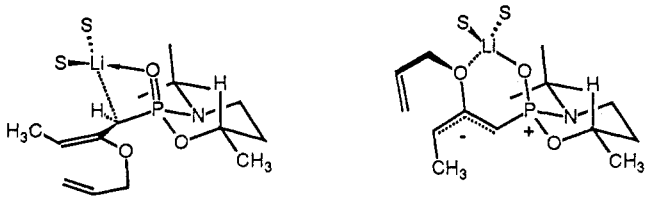
Scheme V



Finally, *the striking effect of added LiCl*[2c] *on the stereoselectivity of the CACR* is illustrated in entries 1 and 2.

To gain more information about the origin of the selectivity and the structure of the anion, we wanted to examine the effect of LiCl and also needed to establish the *sense* of asymmetric induction. Since **3** is racemic and noncrystalline it was not possible to relate the configurations of the stereogenic phosphorus and carbon atoms. For this purpose we employed chiral, nonracemic **2**, Table II. Comparison of the anionic and thermal rearrangements again showed a significant accelerating influence of the negative charge. A systematic examination of the effect of LiCl (entries 1–5) was undertaken. The response in selectivity[14] with various amounts of LiCl suggests a direct involvement of Li^+ in the anion structure and that a competition with the potassium ions is present. This proposal is supported by the high selectivity in a rearrangement with LiDMSO generated from *n*-BuLi (entry 6). Interestingly, added LiCl has no effect on the selectivity of the thermal rearrangement (entry 8). Finally the 2*R*,6*S* isomer *trans*-**2** rearranged with high selectivity as well (entry 9).

The absolute sense of the asymmetric induction was determined by oxidative degradation of the rearrangement products. As shown in Scheme V, *cis*-**4**[7] produced (*S*)-dimethyl methylsuccinate and *trans*-**4**[7] produced the *R* antipode.[15] Since both substrates **2** had the *E* configuration of the enol ether double bond, we can unambiguously assign the *sense* of chair-like folding of the allyl vinyl ether



I II

Figure 1. Two limiting proposals for rearrangement transition state (S = solvent).

in the rearrangement. Thus, in *cis*-**2**, the rearrangement proceeds by bonding to the *re* face while in *trans*-**2** the opposite folding to the *si* face is observed.

From these results it is clear that the high levels of asymmetric induction can be obtained in the CACR and that the selectivity is unique to special properties of the anion. Since we have established the absolute configurations of the educt and product, it is of interest to speculate on the structure of the anionic intermediate which would be most compatible with the observed correlation. Two proposals of limiting structures for Li^+, *cis*-2^- are shown in Figure 1. The key features common to these structures, a planar carbanion and strong polarization of the phosphorus–oxygen bond, are consistent with the available spectroscopic data on related P-stabilized anions.[16] In I the anion conformation is determined by the ligand structure and is fixed by Li^+ coordination. The chair folding then corresponds to a formal *anti* S_E' substitution.[17]

(15) The configurations of the methylsuccinates was established by comparison of their 500-MHz ^1H NMR spectra in the presence of (*R*)-9-(trifluoromethyl)anthrylcarbinol[15a] with authentic samples of the enantiomers.[15b] (a) Pirkle, W. H.; Hoover, D. J. In "Topics in Stereochemistry"; Eliel, E. L., Allinger, N. L., Wilen, S. H., Eds.; Wiley: New York, 1983; Vol. 13, pp 280–298. (b) Cohen, D. G.; Milovanovic, A. *J. Am. Chem. Soc.* **1968**, *90*, 3495.

(16) (a) Bottin-Strzalko, T.; Seyden-Penne, J.; Pouet, M.-J.; Simonnin, M.-P. *J. Org. Chem.* **1978**, *43* 4346. (b) Bottin-Strzalko, T.; Corset, J.; Froment, F.; Pouet, M.-J.; Seyden-Penne, J.; Simonnin, M.-P. *Ibid.* **1980**, *45*, 1270. (c) Corset, J. *Pure Appl. Chem.* **1986**, *58*, 1133 and references therein.

In II the anion conformation is determined *and* fixed by Li^+ coordination and the chair folding is determined by the ligand structure. Both of these structures are consistent with the production of (*R*)-dimethyl methylsuccinate from *trans*-4.

In summary, we have demonstrated the potential of chiral-auxiliary-modified, phosphorus-stabilized anions to control the stereochemical course of the CACR with a high level of induction. Application of this concept to other carbon–carbon bond forming reactions, auxiliary optimization, and investigations of anion structure are under active study.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the partial support of this research. This work was supported in part by the University of Illinois Mass Spectrometry Laboratory (PHS HHS GM-27029). We Thank Professor David A. Evans for providing authentic samples of the (*R*)- and (*S*)-methylsuccinates and Professor William H. Pirkle for helpful discussions. J.E.M. thanks the U.S. Air Force Institute of Technology for financial support.

(17) For a recent discussion of the S_E' stereochemistry of allylsilanes and allylstannanes, see: (a) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99. (b) Young, D.; Kitching, W. *Aust. J. Chem.* **1985**, *38*, 1767.

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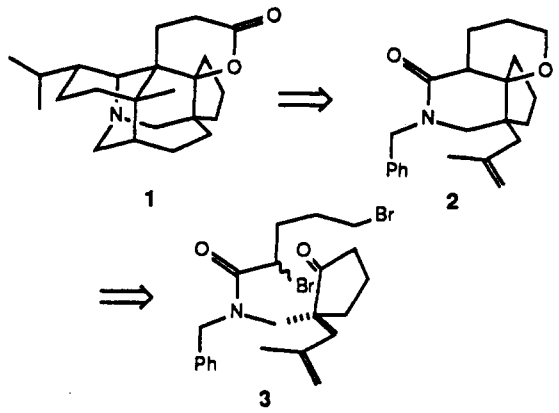
Synthesis of Polycyclic Lactam and Lactone Ethers by Intramolecular Reformatsky Reactions. A Model for Construction of the Daphnilactone A Ring System

Summary: Keto amide **3** is transformed by activated zinc in THF, followed by the addition of HMPA, into tricyclic lactam ether **2**. Lactones **12** and **16** have been prepared by similar reactions.

Sir: Our synthetic plan for the total synthesis of the hexacyclic *Daphniphyllum* alkaloid daphnilactone A (**1**)[1,2] proceeds through lactam ether **2**, which could arise through a bis-annulation reaction involving an intramolecular Reformatsky reaction of **3**. In this paper, we report the successful demonstration of this strategy and its application to the similar preparation of several other polycyclic lactam and lactone ethers.

As shown in Scheme I, deprotonation of unsaturated ester **4**[3] with potassium bis(trimethylsilyl)amide and alkylation of the resulting enolate with methallyl chloride provides **5** (95%), which is treated with lithium benzylamide in THF to obtain amide **6** (95%). Reduction of this material with diisobutylaluminum hydride affords amine

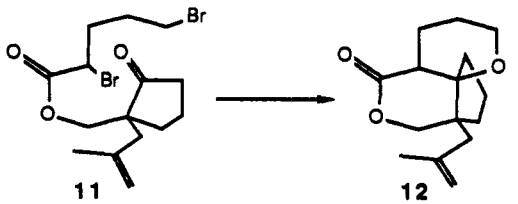


1 **2** **3**

7 (85%), which is coupled with acyl bromide **8** (obtained by the reaction of δ-valerolactone with phosphorus and bromine).[4] After acidic hydrolysis, keto amide **3** is obtained in 90% yield. If the sequence is carried out without chromatographic purification of the sensitive intermediate enol ethers, compound **3** is obtained in 85% overall yield from **4**.

Treatment of **3** with activated zinc[5] in THF at 0 °C gives hydroxy lactam **10** in 50% yield (Scheme II). Attempts to cause the intermediate zinc aldolate **9** to cyclize to **2** by the use of longer reaction times or higher temperatures were unsuccessful. However, **10** is smoothly cyclized to **2** (90%) by potassium *tert*-butoxide in *tert*-butyl alcohol. Alternatively, **2** is obtained in a one-pot process by treatment of **3** first with activated zinc in THF at 0 °C then with 4 equiv of hexamethylphosphoric triamide (HMPA). After 2 h at room temperature, tricyclic lactam ether **2** is obtained in 73% yield.

To further define the scope of the bis-annulation reaction, we prepared dibromo ester **11** by reducing **5** with lithium aluminum hydride to give a primary alcohol (75%), which is coupled with acyl bromide **8**. After acidic hydrolysis of the enol ether, ester **11** is obtained in 80% yield. Treatment of **11** with activated zinc in THF at 0 °C, addition of 4 equiv of HMPA, and stirring at room temperature gives the crystalline lactone ether **12** (mp 86–88 °C) in 64% yield.



11 **12**

At this point, we have not established the stereochemistry of lactam ether **2** or lactone ether **12**. Both reactions are stereoselective, yielding only one isomeric product. When the Reformatsky reactions of **3** or **11** are carried out in THF and the β-hydroxy esters are isolated, only one stereoisomer is obtained in each case. On purely intuitive grounds, it is likely that the bicyclo[4.3.0]nonane system is cis-fused in both products. For the purpose of our projected daphnilactone A synthesis, the mode of fusion of the bicyclo[4.4.0]decane moiety is not important, since the stereocenter α to the carbonyl group is destined to be alkylated at a later stage in the synthesis.

More light was shed on the stereochemistry of the process by the reaction of dibromo ester **13**, prepared from 2,2-dimethyl-1,3-propanediol by acylation with **8** (81%)

(1) Yamamura, S.; Hirata, Y. *Alkaloids (N.Y.)* **1975**, *15*, 41.
(2) For previous work on the total synthesis of *Daphniphyllum* alkaloids, see: (a) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650. (b) Orban, J.; Turner, J. W. *Tetrahedron Lett.* **1983**, *24*, 2697.
(3) Smith, A. B., III.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Woukulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.
(4) Isenberg, N.; Barkocy, I.; Parker, S. R. *Angew. Chem.* **1963**, *75*, 1205.
(5) Arnold, R. T.; Kulenovic, S. T. *Synth. Commun.* **1977**, *7*, 223.

0022-3263/87/1952-5745$01.50/0