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.

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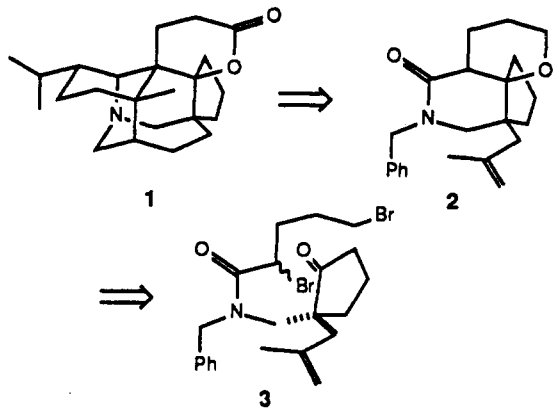
Synthesis of Polycyclic Lactam and Lactone Ethers by Intramolecular Reformatsky Reactions. A Model for Construction of the Daphnilactone A Ring System

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

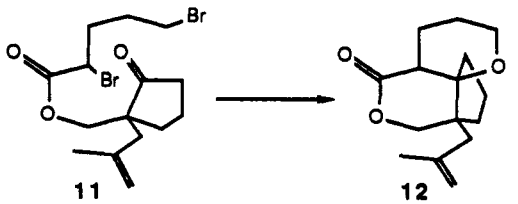


1 **2** **3**

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.
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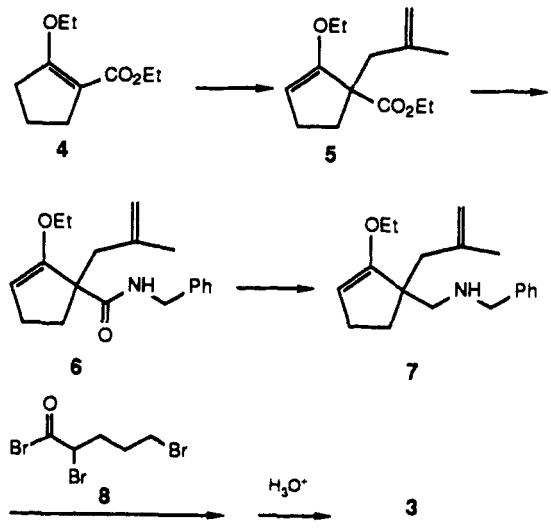
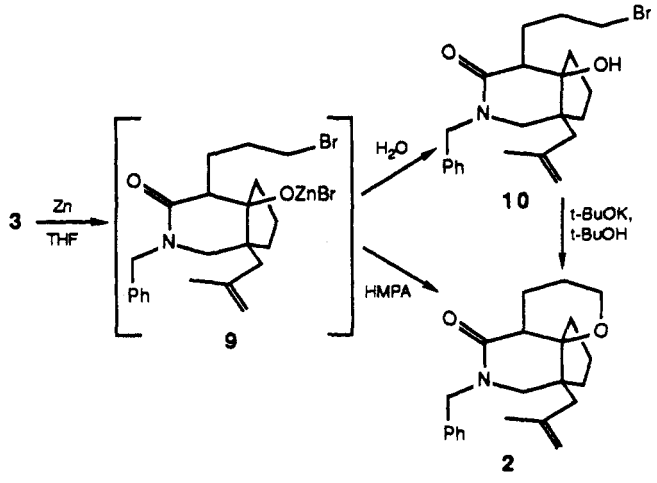
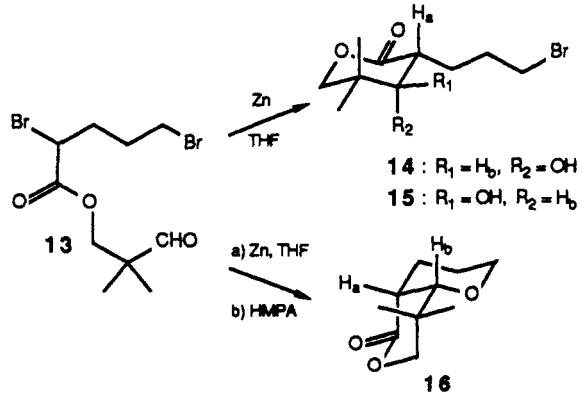
Scheme I



Scheme II



Scheme III



followed by oxidation of the resulting monoester with pyridinium dichromate in CH_2Cl_2 (62%). As shown in Scheme III, treatment of **13** with activated zinc in THF affords two β-hydroxy lactones, **14** and **15**, in a ratio of 6:1 and a total yield of 55%. The stereostructures of these materials were assigned on the basis of the observed H_a–H_b coupling constants, 3.4 Hz for **14** and 9.2 Hz for **15**. When the Reformatsky reaction is carried out in an identical manner, 4 equiv of HMPA is added, and the reaction kept at room temperature for 2 h before workup, lactone ether **16** (mp 80–81 °C) is obtained in 58% yield, along with 12% of an equimolar mixture of **14** and **15**. The structure of **16** derives from the H_a–H_b coupling constant of 2.6 Hz.

A final point to note is that our results with **13** show that the aldolate corresponding to **14** undergoes the intramolecular alkylation reaction substantially faster than does the aldolate corresponding to **15**. Further experiments to define the scope of the intramolecular Reformatsky reaction and its utility in the synthesis of polycyclic systems are underway.

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Supplementary Material Available: Synthetic procedure used to convert amide **3** into lactam **2** and complete spectral data for compounds **2**, **3**, **5**–**8**, and **11**–**16** (5 pages). Ordering information is given on any current masthead page.

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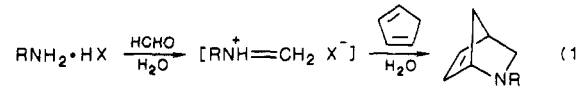
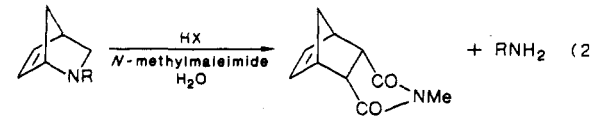
Immonium Ion Based Synthetic Methodology: A Novel Method for the N-Methylation of Dipeptides and Amino Acid Derivatives via Retro Aza Diels–Alder Reactions

Summary: A novel method for the N-methylation of amino acid derivatives and dipeptides is detailed that features facile room-temperature retro Diels–Alder reactions of N-substituted 2-azanorbornenes with trapping of the incipient immonium ion with triethylsilane/trifluoroacetic acid.

Sir: It has been shown that immonium ions generated in situ from primary alkylamines, acid, and aqueous formaldehyde in water undergo a facile cyclocondensation with cyclopentadiene at room temperature (cf. eq 1).[1] More



recently we have demonstrated that 2-azanorbornenes undergo smooth acid-catalyzed heterocycloreversion in water at ambient temperature in the presence of *N*-methylmaleimide (cf. eq 2).[2] It occurred to us that the



extremely mild reaction conditions employed in eq 1 and 2 coupled with the compatibility of the chemistry illustrated with functional groups would permit access to N-methylated amino acid derivatives and small peptides provided the immonium ion species generated during the

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