of renin inhibitors.[14] Future reports will describe the application of this strategy to synthesis of inhibitors of other proteolytic enzymes.

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Supplementary Material Available: Experimental data for **2**, **3**, **13A,B**, **15**, **16A,B**, **17A,B**, **18A,B**, **19**, and **20** (16 pages). Ordering information is given on any current masthead page.

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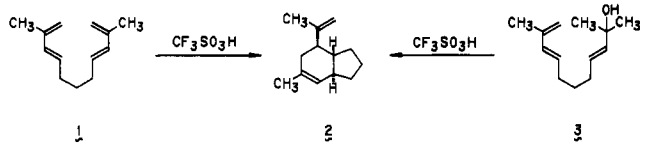
Control of Regiospecificity in Ionic Diels-Alder Reactions. The Use of Allylic Alcohols and Allylic Ethers as Precursors of Dienophilic Allyl Cations

Summary: Allylic alcohols and allylic ethers have been used as precursors of allyl cations in an intramolecular "ionic Diels-Alder reaction" in order to gain complete control of the regiochemistry of the cycloaddition.

Sir: Recently, we demonstrated that both intramolecular[2] and intermolecular[3] 2 + 4 cycloaddition reactions of allyl cations to 1,3-dienes could be accomplished at low temperature in high yield and with excellent stereospecificity.[4] This "ionic Diels-Alder reaction" is exemplified by the intramolecular cyclization of **1** to **2** in 88% yield using trifluoromethanesulfonic (triflic) acid as a catalyst. Due



1 2 3

to the symmetry of **1**, protonation of either diene produces the same allyl cation. However, in an unsymmetrical tetraene, a complication exists because the site of initial protonation, which determines which portion of the molecule becomes the allyl cation (dienophile), cannot be rigorously controlled. In order to circumvent this problem, we sought other precursors for the allyl cation portion of the intermediate leading to **2**. We now wish to report that intramolecular ionic Diels-Alder reactions may be accomplished in high yield, stereospecifically and regiospecifically, through the use of allylic alcohols or allylic ethers as specific allyl cation precursors.

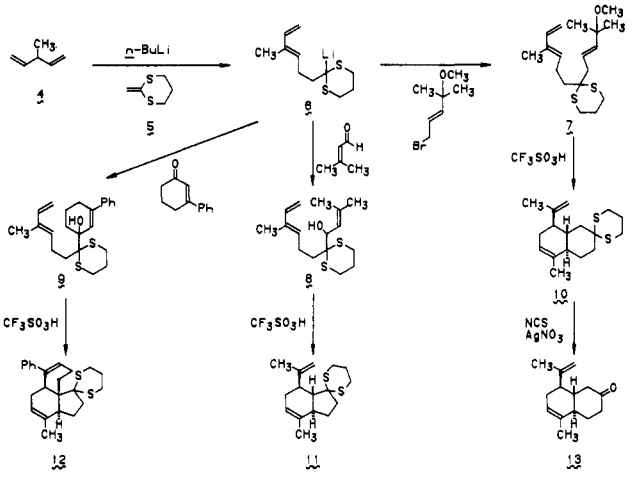
Table I. Yields and Reaction Conditions for the Intramolecular Ionic Diels-Alder Reaction of 7-9

substrate	catalyst,[a] mol %	conditions: temp, °C	conditions: time, min	product	% yield
7	12[b]	10	20	**10**	31
8	37[b]	25	15	**11**	56
9	5	−23	2	**12**	80

[a] The triflic acid catalyst was added as a freshly prepared solution in 1,1,2-trichlorotrifluoroethane. [b] The catalyst was added in three equal portions at 5-min intervals.

In order to establish the plausibility of our approach, we first studied the intramolecular cyclization of **3**.[5,6] As previously observed with **1**,[2] triflic acid was an excellent catalyst for cyclization. Treatment of a dilute solution of **3** in methylene chloride with 5 mol % of triflic acid for 20 min at −23 °C gave a 77% yield[6] of **2** (98% isomeric purity). Significantly, no hydroxylic products resulting from capture of water by the intermediate cations were observed.[4b,c] This confirmed the viability of using allylic alcohols as allyl cation precursors in the intramolecular ionic Diels-Alder reaction.

In order to demonstrate the versatility of our approach, a variety of substrates were synthesized and their cyclization was investigated. Treatment of 3-methyl-1,4-pentadiene (**4**) with *n*-butyllithium gave (3-methylpentadienyl)lithium.[9] Addition of 2-methylene-1,3-dithiane (**5**)[10] then generated **6**, which on subsequent addition of appropriate unsaturated electrophiles afforded **7**, **8**, and **9** in 74%, 74%, and 48% yields, respectively.[11,12]



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(5) Treatment of methyl (*E*)-7-oxo-2-heptenoate[7] with the ylide derived from methallyltriphenylphosphonium chloride[8] gave methyl (2*E*,7*E*)-9-methyl-2,7,9-decatrienoate (44% yield). Three successive treatments of this triene with methyllithium gave **3** in 89% yield.

(6) Satisfactory elemental analyses and exact mass molecular weights have been obtained on all new compounds. In all cases, ^1H and ^{13}C NMR and IR spectral data were consistent with the assigned structures.

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(11) This "one-pot" reaction sequence should have extensive utility outside of the examples cited herein.

(12) The *E* stereochemistry of **7-9** was assigned according to the literature methods: Cardenas, C. G. *Tetrahedron Lett.* **1969**, 4013.

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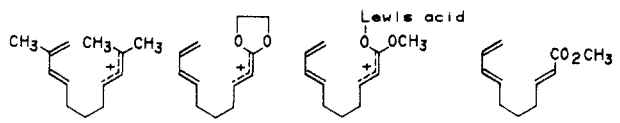
Treatment of **7**, **8**, and **9** with triflic acid in methylene chloride gave **10**, **11**, and **12**, respectively, as the only monomeric fully cyclized products.[13] Reaction conditions and yields are summarized in Table I. As indicated, the reactions are uniformly rapid and stereospecific. These examples give an indication of the potential of the ionic Diels–Alder reaction in the synthesis of diverse polycyclic molecules.

The yield of **10** was low due to problems encountered in its purification. However, when crude **10** was treated with *N*-chlorosuccinimide–silver nitrate in acetonitrile–water,[14] **13** was obtained in 34% overall yield from **7**. This series of reactions provides a quick and stereospecific entry into the cadenane ring system. Selective reduction of the isopropenyl moiety of **13** was accomplished in 79% yield using hydrogen and Wilkinson's catalyst to produce a known precursor[15] of γ_1-cadenene. Compound **11** has the correct stereochemistry to be a precursor of systems related to oplopanone.[16] Thus, a variety of naturally occurring ring systems are readily accessible via our sequence of reactions.

An analogy may be drawn between our results and those of Roush with Lewis acid and hydrofluoric acid catalyzed and uncatalyzed intramolecular Diels–Alder reactions.[17] The proposed reactive intermediates are illustrated by **14**–**17**. Ions **14**–**16** cyclize to form only trans-fused



14 **15** **16** **17**

products; **17** produces a mixture of trans- and cis-fused products. Our ionic Diels–Alder reaction would appear to involve the extreme of a continuum of transition states for the Diels–Alder reaction.[18] This continuum can be viewed as an ordering of reactions that utilize as dienophiles allyl cations (i.e., **14**), dioxolenium ions (i.e., **15**), Lewis acid complexed carbonyl derivatives (i.e., **16**), olefins bearing uncharged electron-withdrawing groups (i.e., **17**), and unactivated olefins.[19]

We are continuing to investigate the synthetic and mechanistic implications of these ionic cycloaddition reactions.

Acknowledgment. We are indebted to the National Science Foundation and to the General Medical Institute of the National Institutes of Health for grants which supported this investigation.

Registry No. **2**, 91993-46-3; **3**, 102871-00-1; **4**, 1115-08-8; **5**, 21777-31-1; **6**, 102871-01-2; **7**, 102871-02-3; **8**, 102871-03-4; **9**, 102871-04-5; **10**, 102871-05-6; **11**, 102871-06-7; **12**, 102871-07-8; **13**, 102871-08-9; (*E*)-1-bromo-4-methoxy-2-pentene, 102870-99-5; 3-methyl-2-butenal, 107-86-8; 3-phenyl-2-cyclohexenone, 10345-87-6.

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(13) The stereochemistry of **13** (and thus of **10**) was assigned from H_{4a}–H_{8a} and H_8–H_{8a} couplings of 11 Hz, as determined by a combination of multiple Eu(fod)$_3$-induced shift experiments and multiple spin-decoupling experiments. The stereochemistry of **11** was determined by deprotection to the ketone (47%), which had H_{3a}–H_{7a} and H_7–H_{7a} coupling constants of 12.4 and 10.6 Hz, respectively. Since the stereochemistry of the single isomer of **12** could not be assigned on the basis of ^{1}H NMR coupling constants, its stereochemistry was tentatively assigned by analogy to that of **2**, **10**, and **11**.

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Oxazoline-Mediated Asymmetric Alkylation of Amines

Summary: Chiral oxazolines serve as readily available auxiliaries for the functionalization of secondary amines and for mediating their alkylation via their conjugate bases, which are dipole-stabilized anions. Both attachment and removal of the chiral auxiliary occur in routinely high yield. *Homochiral* 1-substituted tetrahydroisoquinolines are available as either enantiomer by selection of the appropriate enantiomer of valine, both of which are commercially available.

Sir: The fascinating field of dipole-stabilized anion chemistry was reviewed in 1978.[1] Six years later, another review[2] was devoted exclusively to updating the subject of metalations adjacent to a functionalized nitrogen. Nevertheless, the subject received little or no mention in two recent monographs on carbanions.[3] In spite of the broad interest, successful *asymmetric* amine alkylations via dipole stabilized anions are few. Meyers has demonstrated that formamidines derived from chiral amino alcohols such as (1*S*,2*S*)-(+)-1-phenyl-2-amino-1,3-propanediol[4] or L-valinol[5] give excellent optical yields, which are significantly better than several other chiral amines[6] in the alkylation of tetrahydroisoquinoline formamidines. Recently, Meyers reported on the application of L-valinol derived formamidines to the synthesis of indole alkaloids.[7] Unfortunately, these chiral formamidines are unable to mediate the deprotonation of heterocycles for which the proton adjacent to nitrogen is not also allylic or benzylic.[8]

In entering this field, we hoped to design a system which would accomplish asymmetric alkylation of amines in high chemical and optical yields and which would be applicable to the elaboration of both saturated and allylically activated heterocycles. Our approach to the problem began

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