all respects with the previous sample.

Reaction of 6-(*p*-Tolylsulfonyl)-4,5-decadiene (17) with $Me_3SiC{\equiv}CCH_2Li$. The allenic sulfone **17** (73 mg, 0.25 mmol) was treated with 0.50 mmol of the nucleophile under the same conditions as in entry 12 of the table. The same workup then furnished 87 mg (86%) of enyne **16**, indentical in all respects with the previous sample.

Registry No. **1a**, 86409-85-0; **1b**, 86409-89-4; **1c**, 108895-55-2; **1d**, 108918-97-4; **1e**, 87517-80-4; **2a**, 86409-98-5; **2b**, 86409-95-2; **2c**, 108895-56-3; **2d**, 108895-57-4; **2e**, 87517-81-5; **6**, 108895-58-5; (*E*)-**7**, 108895-59-6; (*Z*)-**7**, 108895-60-9; **8**, 108895-61-0; (*E*)-**9**, 108895-62-1; (*Z*)-**9**, 108895-63-2; **10**, 108895-64-3; **11**, 86409-91-8; **12**, 108895-65-4; **13**, 19542-67-7; **14**, 108895-66-5; **15**, 108895-67-6; **16**, 108895-68-7; **17**, 87517-82-6; $CH{\equiv}CCH_2OSi(Bu\text{-}t)Me_2$, 76782-82-6; $(MeO_2C)_2CH_2$, 108-59-8; $AcCH_2CO_2Et$, 141-97-9; $CH_2(CN)_2$, 109-77-3; $Me_3SiC{\equiv}CMe$, 6224-91-5; $SCH_2S(CH_2)_2CH_3$, 505-23-7; KCN, 151-50-8; NO_2Me, 75-52-5; Ac_2CH_2, 123-54-6; 1-hexyne, 693-02-7.

Sulfur-Bridged Cyclodecenones from Thioaldehyde Diels–Alder Adducts

E. Vedejs,* C. L. Fedde, and C. E. Schwartz

S. M. McElvain Laboratory of Organic Chemistry, Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706

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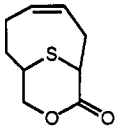
The adduct **7** of cyanothioformaldehyde with 2-(*tert*-butyldimethylsiloxy)-1,3-butadiene has been converted into allylic halides **15** and **20**. Upon heating with $NaI/K_2CO_3/CH_3CN$, the halides alkylate sulfur internally. The resulting sulfonium salts are deprotonated to give the ylides **30** or **28**, and 2,3-sigmatropic rearrangement affords the title compounds **21–23**. In the case of **20**, a single sulfur-bridged *Z*-cyclodecenone **23** is formed in 90% yield, while **15** gives a mixture of olefin *E,Z* isomers. This difference is attributed to conformational preferences of the more highly substituted olefin in ylide **28**. Efficient conversion of **23** into the monocyclic (*Z*)-4-methyl-8-(methylthio)cyclodec-4-enone (**25**) by S-methylation and zinc reduction is also reported.

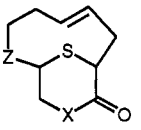
Medium-sized rings are accessible from cyclic sulfides by reactions that bridge the α and α' carbons of the sulfide with a carbon chain.[1-3] One technique for achieving this result is illustrated by the 2,3-sigmatropic shift of bicyclic sulfonium ylides **2** derived from sulfides **1**. The rearrangements to sulfur-bridged lactones **3** or **4** are interesting in the context of ylide stereochemistry and in principle could be used to make the parent medium rings by cleavage of carbon–sulfur bonds. However, the yields of

1 a X = O, Z = CH_2; b X = O, Z = bond; c X = CH_2, Z = CHOAc; d X = CH_2, Z = bond

2



3



4 X = O, Z = bond

5 X = CH_2, Z = CHOAc

3 or **4** are not high enough for preparative applications.[3] Somewhat better results are obtained with a carbocyclic periphery in the ylide, and **2c** affords the bridged cycloundecenone **5** in 60% yield.[2b] This technique has also been applied to highly complex substrates for cytochalasin synthesis with similar efficiency in the ring-expansion step.[2a] Further extensions to sulfur-bridged 10-membered carbocycles are of interest in the context of terpenoid target structures having the cyclodecane skeleton. To evaluate the potential of this approach, we have examined two representative substrates, which are the subject of this paper.

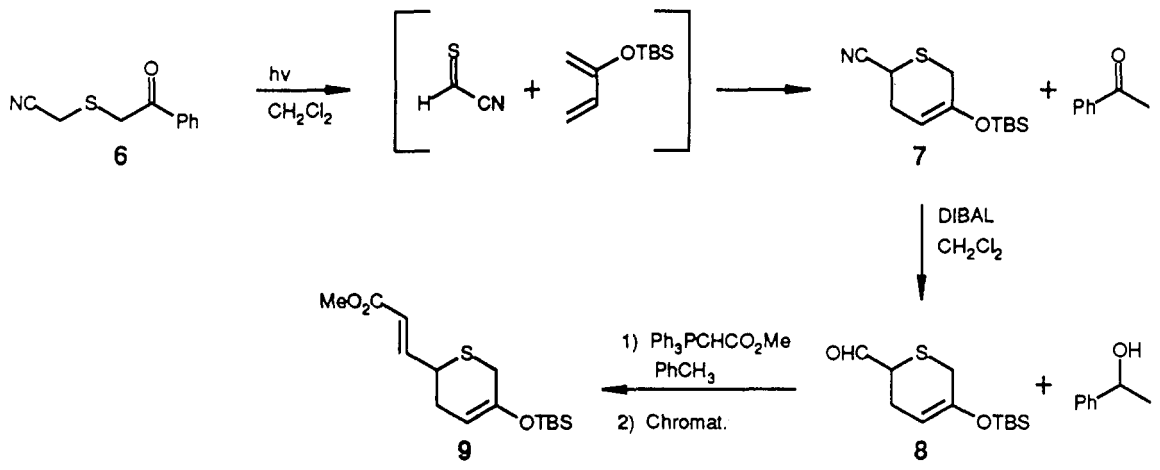
Previous efforts had not been able to identify the variables responsible for the relatively efficient rearrangement of **2c** vs. lactones **2a,b** (60% yield vs. 30%). Difficulties with **2a,b** could have been due to the sensitivity of the bridged, somewhat strained product to the reaction conditions (K_2CO_3/CH_3CN at 70 °C).[3] However, there remained the possibility that the improved behavior of **2c** was anomalous due to some conformational effect of the acetoxy substituent that had been incorporated to approximate the functionality of intermediates in cytochalasin synthesis.[2] To rule out this possibility in the 10-membered carbocycle series, we opted to study the unsubstituted ylide **2d**.

Preparation of starting materials begins with the known thioaldehyde adduct **7** (from NCCH=S + 2-siloxybutadiene).[4] A slight variation of the previously described method via photochemically induced fragmentation of phenacyl sulfide **6** was necessary for preparative-scale synthesis of **7**. The original method used tediuos chromatographic purification to remove acetophenone. To avoid this procedure, the mixture of **7** + acetophenone was reduced to aldehyde **8** (+ 1-phenylethanol) and converted into the Wittig product **9** without purification of inter-

(1) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358.
(2) (a) Vedejs, E.; Reid, J. D. *J. Am. Chem. Soc.* **1984**, *106*, 4617. (b) Vedejs, E.; Arnost, M. J.; Eustache, J. M.; Krafft, G. A. *J. Org. Chem.* **1982**, *47*, 4384.
(3) Vedejs, E.; Gapinski, D. M.; Hagen, J. P. *J. Org. Chem.* **1981**, *46*, 451.
(4) Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, C. E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556.

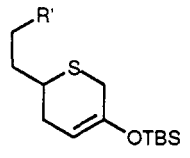
0022-3263/87/1952-4269$01.50/0

Scheme I

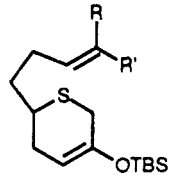


mediates. This variation gave an overall 50% yield of **9** from **6** after simple filtration chromatography (Scheme I).

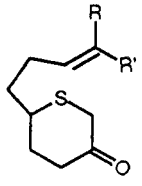
Further conversion into the precursor of ylide **2d** required redox manipulations and chain extension. First, the conjugated enoate double bond was reduced (Red Al/CuBr)[5] to give **10**. Carefully controlled DIBAL reduction at −78 °C (toluene) then gave the aldehyde **11** in 89–95% yield. Subsequent Wittig coupling with $Ph_3P{=}CHCO_2Me$ introduced the necessary carbon chain, and conventional steps efficiently converted the resulting **12** into an allylic chloride **15** via **13** (by DIBAL reduction of **12**) and the keto alcohol **14** (from **13** + $Et_3HN^+ {}^-F$). A similar sequence gave the analogous allylic chloride **20** having a trisubstituted double bond. In this series, the chain extension from aldehyde **11** required use of the Horner–Emmons reagent **16**[6] for good results. The product **17** was contaminated with ca. 5% of the *Z* isomer, but **17** was readily purified, and the remaining intermediates to **20** retained the *E*-olefin geometry. In an earlier study, the preparation of **9** by the Diels–Alder trapping of the thioacrolein derivative $EtO_2CCH{=}CHCH{=}S$ was described.[4] Although this is a more direct sequence than that described above, it is not as efficient due to the high self-condensation reactivity of the unsaturated thioaldehyde.

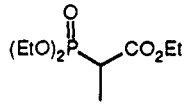


10 R' = CO_2Me
11 R' = CHO



12 R = H, R' = CO_2Me
13 R = H, R' = CH_2OH
17 R = CH_3, R' = CO_2Et
18 R = CH_3, R' = CH_2OH

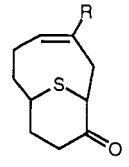


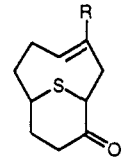


16

14 R = H, R' = CH_2OH
15 R = H, R' = CH_2Cl
19 R = CH_3, R' = CH_2OH
20 R = CH_3, R' = CH_2Cl

Conversion of allylic chloride **15** into ring-expansion products occurred smoothly under conditions that promote internal S-alkylation and ylide formation.[2,3] Thus, heating **15** with NaI (to generate the allyl iodide in situ) and K_2CO_3 in acetonitrile (65 °C) resulted in conversion to a 1.6/1 mixture of two medium ring products **21** and **22** in 70% yield. The increased yield relative to the reaction of the analogous lactone sulfide **1a** is significant and points to the lactone functionality as the detrimental feature in the latter case.[3] There is also a difference in stereochemistry. The product from **1a** is the *Z*-alkene **3** while **15** gives both *E* and *Z* isomers.





21 R = H
23 R = CH_3

22 R = H

The corresponding reaction of the trisubstituted double bond analogue **20** proved to be the most efficient. Treatment with NaI/K_2CO_3 as before gave a single product **23** in 88–93% isolated yield. In contrast to the disubstituted alkenes **21** and **22**, the alkene geometry of **23** was not obvious from simple ^1H NMR spectra. However, irradiation of the olefinic CH_3 group caused a 13% NOE enhancement of the adjacent vinyl C–H signal, thereby establishing the *Z*-olefin geometry.

The periphery of **23** corresponds to a (*Z*)-4-methyl-4-cyclodecenone. To demonstrate the ease of sulfur bond cleavage for possible synthetic applications, **23** was treated with the Meerwein reagent $Me_3O^+BF_4^-$ followed by Zn/HOAc reduction of the sulfonium salt **24**.[2a] This procedure gave a single cyclodecenone product **25** in 90% yield.

Discussion

The improved yields from the sulfur-bridging reactions of **15**, and especially of **20**, are consistent with the internal alkylation–ylide rearrangement pathway as shown. Direct cyclization from an enolate **26** is ruled out in the case of **20** because the double-bond geometry in the product is inverted relative to that in **20**. This can only occur via

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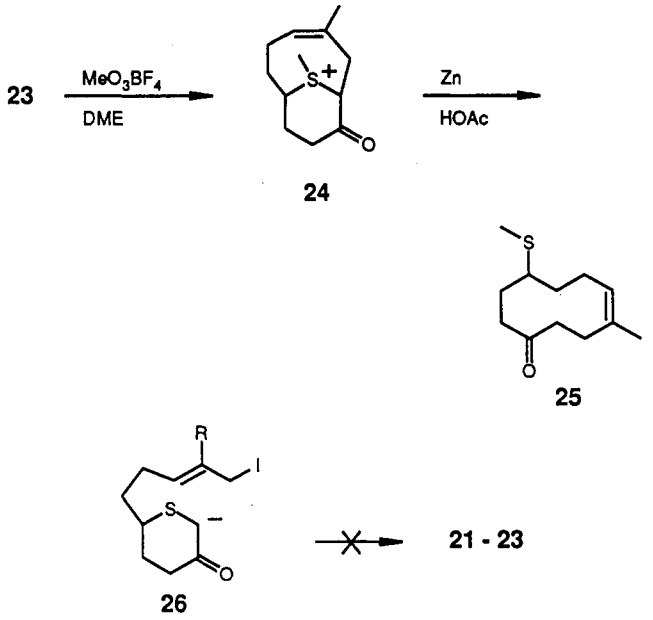
(6) Bodnarchuk, N. D.; Malovik, W.; Derkach, G. I. *Zh. Obshch. Khim.* **1970**, *40*, 1201.



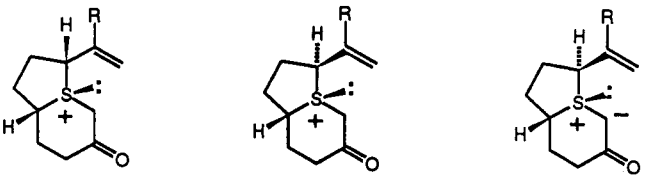
the intervention of an intermediate such as the sulfonium ylide **28** where olefin E/Z geometry temporarily disappears. Direct enolate cyclization from **26** (R = H) could conceivably be responsible for the formation of the *E*-alkene product **22** from **15**. However, the transition state for this process is unreasonably constrained by the *E*-alkene and by developing transannular interactions. Furthermore, the reaction variables do not resemble the high-dilution conditions that might favor such a process, and the ylide mechanism has extensive analogy.[1-3]

In simpler ylide rearrangements involving bicyclic transition states, the formation of the *Z*-olefin in eight-membered ring products has been associated with an ylide precursor having cis alkenyl and ylide groups relative to the sulfur-containing ring.[1,7] In the present case involving a tricyclic transition state, the additional geometric constraints require a related geometry **28**. This, in turn, requires a sulfonium salt stereochemistry as in **27**, resulting from internal sulfur alkylation, to give a cis-fused bicyclic unit. Other conformations of the propenyl substituent are possible in **28**, but the cisoid rotamer shown must be responsible for the *Z*-alkene product. No other combination of ylide sulfur stereochemistry and propenyl stereochemistry or conformation can reasonably produce the observed *Z*-alkene product by concerted rearrangement due to an unfavorable distance between the ylide carbon and the propenyl terminus. On the other hand, a transoid ylide rotamer **29** does have the geometry required for rearrangement to an *E*-alkene. No *E*-olefin product is observed starting from **20**, but the related reaction of **15** does produce both *Z* and *E* isomers of **21** and **22** even though **22** is severely strained (judging from models).

28 R = CH_3 **29** R = CH_3
30 R = H **31** R = H

A comparison of the two possible ylide rotamers **30** and **31** derived from **15** is revealing. Cisoid **30** must point the vinyl group toward the hindered concave face of the bicyclic sulfonium ring system. Transoid **31** is less hindered and is responsible for nearly 40% of the reaction pathway. In the propenyl system, the situation is different because neither the cisoid **28** nor the transoid propenyl rotamer **29** can avoid steric interactions. The transition state **28** leading to *Z*-alkene is now substantially less strained than is **29**, and only the *Z*-isomer **23** is formed.

There is no evidence regarding the role of other possible diastereomers at sulfur, but this would involve trans-fused bicyclic systems that are strained due to the long C–S bonds. Sulfonium salt diastereomer **32** is also possible with the alternative alkenyl stereochemistry α to sulfur. Geometric constraints would prevent concerted rearrangement of the derived ylide **33** if it was formed. Since the initial



27 **32** **33**

cyclization leading to sulfonium iodide is potentially reversible via nucleophilic attack of iodide, it seems likely that **32** would simply equilibrate with **27** and would eventually drain off to **23** via ylide **28**. In view of the high yield and the absence of byproducts from other ylide decomposition pathways such as Stevens rearrangement,[8] the barrier from **28** to **23** cannot be large.

In conclusion, the sulfur bridging sequence from **20** constitutes an efficient entry into cyclodecenones containing the *Z*-trisubstituted double bond. The improved yield over previously studied sulfur-bridging reactions[2,3] results from several factors. Product stability is probably the main advantage relative to the lactone system (**3**). The absence of an *E*-alkene byproduct in the latter case may simply reflect its increased lability. With regard to analogues having the 11-membered carbocyclic periphery as in **5**, the formation of 10-membered **23** benefits kinetically from the five-center transition state leading to the sulfonium salt **27**, and also from the increased population of the cisoid propenyl rotamer **28**. This combination of factors results in the most efficient sulfur-bridging reaction to date and bodes well for applications in synthesis of cyclodecanone derivatives.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were recorded on either a Bruker WP-200 200-MHz or a Bruker WH-270 270-MHz spectrometer. All chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. Infrared (IR) spectra were recorded on a Beckman Acculab 7 spectrometer with calibration achieved via the 1601.4 cm^{-1} peak of a standard polystyrene film. Mass spectra (high-resolution) were run on a Kratos MS-25 or MS-80 spectrometer.

Dry solvents were obtained as follows: Diethyl ether, tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were distilled from sodium benzophenone; benzene and toluene were distilled from calcium hydride; methylene chloride (CH_2Cl_2) and carbon tetrachloride (CCl_4) were distilled from P_2O_5; acetonitrile (CH_3CN) was distilled from P_2O_5 and redistilled from anhydrous K_2CO_3. Hexane and ethyl acetate were flash-distilled in bulk.

Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed silica gel plates (Merck 60F-254). Preparative thin-layer chromatography (PTLC) was run on glass plates coated 2 mm thick with silica gel (Merck 60PF-254). Column chromatography was done with Davisil 62 60–200-mesh

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silica gel (gel/sample ca. 30/1 by weight). Flash chromatography was done with Merck 60 230–400-mesh silica gel according to the method of Still.[9]

Anhydrous potassium carbonate was obtained by flame drying a fine powder under high vacuum. All reactions were carried out in flame-dried flasks that were cooled under a stream of nitrogen and under a nitrogen atmosphere with positive pressure maintained throughout.

Cyanosiloxythiane 7. Phenacyl sulfide **6** (562 mg, 2.93 mmol) and 2-(*tert*-butyldimethylsiloxy)butadiene (1.30 g, 7.05 mmol) were thoroughly mixed in 50 mL of dry CH_2Cl_2, and the solution was divided into four equal portions, each placed in a 25-mL round-bottom flask equipped with a magnetic stir bar and septum. The flasks were placed in a water-cooling bath consisting of a Pyrex crystallizing dish (150 × 75 mm) containing a copper-tubing cooling coil. This maintained the cooling bath at approximately 28 °C during photolysis. The stirred solutions were photolyzed with a 275-W sun lamp (positioned 1 in. below the cooling bath) under static nitrogen pressure for 7 h. After combination and solvent removal, the residue was eluted through a silica gel column (15 g, 15% ethyl acetate/hexane) to yield 1.30 g of a yellow oil containing thiane **7**[4] and acetophenone. This was carried on without further purification due to the difficulty in separating acetophenone from the cycloadduct. A pure sample was obtained by careful flash chromatography (8% ethyl acetate/hexane) to give 82% **7**: oil; analytical TLC (silica gel F254), 10% ethyl acetate/hexane, R_f 0.22; *m/e*, exact mass calcd for $C_{12}H_{21}O_1N_1Si_1S_1$ 255.1108, found 255.1112, error 1.6 ppm; IR (neat, cm^{-1}) 2210 (CN), 1675 (=CO); 200-MHz NMR ($CDCl_3$, ppm) 4.94–4.91 (1 H, m), 3.66 (1 H, t, J = 4.2 Hz), 3.51 (1 H, br d, J =16.9 Hz), 2.97 (1 H, d, J = 16.9 Hz), 2.75–2.60 (2 H, m), 0.92 (9 H, s), 0.17 (6 H, s).

Unsaturated Ester Thiane 9. The previous mixture of thiane **7** and acetophenone (1.30 g) was dissolved in 20 mL of dry CH_2Cl_2, flushed with nitrogen, and cooled to −78 °C. Diisobutylaluminum hydride (DIBAL; Aldrich, 1.0 M in hexane, 7.0 mL, 7.0 mmol) was added dropwise via cannula and the solution stirred at −78 °C for 2 h. Pentane (20 mL, reagent grade) and 10 mL of 10 M acetic acid were cooled to 0 °C with stirring, and the reaction mixture was added slowly via cannula. After the mixture was stirred for 30 min at 0 °C, the layers were separated. The aqueous phase was extracted with ether (2 × 20 mL), and the combined organics were washed with 15 mL water and added to 30 mL saturated aqueous $NaHCO_3$ at 0 °C, and the solution was stirred for 30 min. The layers were separated, and the organics were washed with brine (2 × 20 mL) and dried ($MgSO_4$). After solvent removal, the residue was eluted through a silica gel plug (15 g, 5% ethyl acetate/hexane) to afford 821 mg of a clear yellow oil as a mix of aldehyde **8** and 1-phenylethanol.

Due to its lability, aldehyde **8** was used without further purification. It was dissolved in 3 mL of dry toluene, and methyl (triphenylphosphoranylidene)acetate (Aldrich, 980 mg, 2.93 mmol) in 12 mL of toluene was added dropwise via cannula. The mixture was stirred for 4 h at room temperature, the solvent removed, and the residue purified by filtration chromatography over silica gel (10 g, 5% ethyl acetate/hexane) to give 498 mg of product **9** as a colorless oil (54% based on phenacyl sulfide **6**): oil; analytical TLC (silica gel F254), 10% ethyl acetate/hexane, R_f 0.54; *m/e*, exact mass calcd for $C_{15}H_{26}O_3Si_1S_1$ 314.1365, found 314.1378, error 4.1 ppm; IR (neat, cm^{-1}) 1735 (C=O), 1685 (=CO), 1665 (C=C); 200-MHz NMR ($CDCl_3$, ppm) 6.97 (1 H, dd, J = 15.6, 6.6 Hz), 5.92 (1 H, dd, J = 15.6, 1.4 Hz), 4.94 (1 H, br, t, J = 4.3 Hz), 3.72 (3 H, s), 3.48 (1 H, dddd, J = 6.2, 6.2, 6.2, 1.3 Hz), 3.04 (1 H, br d, J =16.9 Hz), 2.97 (1 H, br d, J =16.9 Hz), 2.59 (1 H, br d, J = 17.9 Hz), 2.39 (1 H, br d, J = 17.9 Hz), 0.89 (9 H, s), 0.12 (6 H, s).

Saturated Ester Thiane 10. To copper bromide (Aldrich, 330 mg, 2.30 mmol) in a flame-dried, nitrogen-flushed round-bottom flask equipped with a septum and stir bar was added 2 mL of dry THF. The suspension was cooled to 0 °C, and sodium bis(2-methoxyethoxy)aluminum hydride (Red Al, Aldrich; 3.4 M in toluene, 0.67 mL, 2.28 mmol) was added rapidly via syringe.[5] After stirring for 30 min at 0 °C, the black, heterogeneous mixture was cooled to −78 °C, and *sec*-butanol (Shell, dried over $MgSO_4$, distilled, 0.50 mL, 5.46 mmol) was added rapidly. Within 2 min, the unsaturated ester **9** (143 mg, 0.46 mmol) in 1 mL THF was added via cannula. After 10 min, the reaction was warmed to and kept between −20 to −40 °C for 1.5 h. The reaction was quenched with 2 drops of water; the mixture became very thick. It was transferred to a separatory funnel containing 10 mL of saturated NH_4Cl. After separation of the phases, the clear and nearly colorless organic layer was washed with brine (2 × 25 mL) and dried ($MgSO_4$). The solvent was removed after filtration to afford a pale yellow oil that was purified by PTLC (20% ethyl acetate/hexane, R_f 0.57), yielding 133 mg (92%) of product **10**: oil; *m/e*, exact mass calcd for $C_{15}H_{28}O_3Si_1S_1$ 316.1521, found 316.1518, error 1 ppm; IR (neat, cm^{-1}) 1745 (C=O), 1675 (=CO); 200-MHz NMR ($CDCl_3$, ppm) 4.97–4.87 (1 H, m), 3.66 (3 H, s), 3.17 (1 H, br d, J = 16.7 Hz), 2.88 (1 H, br d, J = 16.7 Hz), 2.76–2.53 (1 H, m), 2.51–2.41 (3 H, m), 2.21–2.01 (1 H, m), 1.96–1.75 (2 H, m), 0.90 (9 H, s), 0.13 (6 H, s).

Aldehyde Thiane 11. The ester **10** (76.0 mg, 0.24 mmol) was dissolved in 2 mL of dry toluene and cooled to −78 °C. DIBAL (Aldrich, 1.0 M in hexane, 0.28 mL, 0.28 mmol) was added dropwise via syringe. After it was stirred for 8 min, the solution was transferred rapidly via cannula to a stirred −78 °C mixture of ether (20 mL) and methanol (Mallinckrodt anhydrous, 1 mL). This was stirred an additional 5 min, transferred to a separatory funnel with ether, and washed with saturated NH_4Cl (3 × 5 mL) and brine (10 mL), and the organics were dried ($MgSO_4$). Solvent removal afforded an oil that was eluted on a small plug of silica gel (1 g, $CHCl_3$) to yield 65.0 mg (94%) of aldehyde **11**: oil; analytical TLC (silica gel F254), 20% ethyl acetate/hexane, R_f 0.41; *m/e*, exact mass calcd for $C_{14}H_{26}O_2Si_1S_1$ 286.1416, found 286.1402, error 4.9 ppm; IR (neat, cm^{-1}) 1730 (C=O), 1680 (=CO); 200-MHz NMR ($CDCl_3$, ppm) 9.79 (1 H, s), 4.91 (1 H, t, J = 4.4 Hz), 3.11 (1 H, br d, J = 14.0 Hz), 2.89 (1 H, d, J = 14.0 Hz), 2.76–2.54 (3 H, m), 2.54–2.39 (1 H, m), 2.21–2.04 (1 H, m), 2.04–1.52 (2 H, m), 0.92 (9 H, s), 0.08 (6 H, s).

Unsaturated Ester Thiane 12. The aldehyde **11** (49.3 mg, 0.16 mmol) and methyl (triphenylphosphoranylidene)acetate (Aldrich, 104.2 mg, 0.31 mmol) were dissolved in 10 mL of dry THF and heated to reflux for 4 h. After the solution was cooled, the solvent was removed and the residue purified by flash chromatography on silica gel (5% ethyl acetate/hexane) to yield 46.6 mg (87%) of thiane **12**: oil, analytical TLC (silica gel F254), 20% ethyl acetate/hexane, R_f 0.60; *m/e*, no peak match, parent; formula $C_{17}H_{30}O_3Si_1S_1$; IR (neat, cm^{-1}) 1730 (C=O), 1680 (=CO), 1660 (C=C); 200-MHz NMR ($CDCl_3$, ppm) 6.94 (1 H, dt, J = 15.6, 6.9 Hz), 5.84 (1 H, dt, J = 15.6, 1.4 Hz), 4.97–4.87 (1 H, m), 3.71 (3 H, s), 3.20 (1 H, br d, J = 17.1 Hz), 2.86 (1 H, d, J = 17.1 Hz), 2.80–2.66 (1 H, m), 2.46–2.29 (3 H, m), 2.20–2.06 (1 H, m), 1.69 (2 H, ddd, J = 7.4, 7.4, 7.4 Hz), 0.88 (9 H, s), 0.11 (6 H, s).

Allylic Alcohol Thiane 13. The unsaturated ester **12** (46.6 mg, 0.14 mmol) was dissolved in 5 mL of dry THF and cooled to −78 °C. DIBAL (Aldrich, 1.0 M in hexane, 0.34 mL, 0.34 mmol) was added dropwise via syringe. After it was stirred for 15 min, the reaction mixture was diluted with ether (15 mL) and washed with saturated NH_4Cl, and the organics were dried ($MgSO_4$). Solvent removal yielded an oil that was eluted through a small plug of silica gel ($CHCl_3$) to yield 40.7 mg (95%) of allylic alcohol **13**: oil; analytical TLC (silica gel F254), 20% ethyl acetate/hexane, R_f 0.26; *m/e*, no peak match, parent; formula $C_{16}H_{30}O_2Si_1S_1$; IR (neat, cm^{-1}) 3320 (OH), 1675 (=CO); 200-MHz NMR ($CDCl_3$, ppm) 5.70–5.64 (2 H, m), 4.96–4.88 (1 H, m), 4.06 (2 H, br d, J = 1.0 Hz), 3.21 (1 H, br d, J = 16.9 Hz), 2.84 (1 H, d, J = 16.9 Hz), 2.75–2.69 (1 H, m), 2.45–2.34 (1 H, m), 2.24–2.09 (3 H, m), 1.81 (1 H, br s), 1.61 (2 H, ddd, J = 7.4, 7.4, 7.4 Hz), 0.89 (9 H, s), 0.11 (6 H, s).

Keto Allylic Alcohol 14. The silyl enol ether **13** (40.7 mg, 0.13 mmol) was dissolved in 5 mL of methanol (Mallinckrodt anhydrous) and 0.10 mL of dry THF, and 0.20 mL triethylammonium hydrofluoride was added. The reaction mixture was stirred for 17 h at room temperature and transferred to a separatory funnel with ether (15 mL). The organics were washed with brine (5 mL), the brine was back-extracted with ether (1 mL), and the combined organics were dried ($MgSO_4$). The solvent was removed and the residue purified via PTLC (50% ethyl acetate/hexane, R_f 0.25) to afford 22.4 mg (86%) of keto alcohol **14**: oil; *m/e*, no peak match, parent; formula $C_{10}H_{16}O_2S_1$: IR (neat,

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cm^{-1}) 3400 (OH), 1715 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 5.80–5.56 (2 H, m), 4.09 (2 H, br s), 3.33 (1 H, d, J = 12.9 Hz), 3.14–2.98 (1 H, m), 3.03 (1 H, br d, J = 12.9 Hz), 2.48–2.38 (3 H, m), 2.20–2.12 (3 H, m), 1.66 (2 H, ddd, J = 7.4, 7.4, 7.4 Hz), 1.46 (1 H, br s).

Keto Allylic Chloride 15. Tri-*n*-butylphosphine (Aldrich, 0.024 mL, 0.094 mmol) was added with stirring to 1 mL of dry CCl_4 in a flame-dried round-bottom flask. The solution was cooled to 0 °C and the alcohol **14** (9.4 mg, 0.047 mmol) in 1 mL of CCl_4 added dropwise via cannula. The ice bath was removed, and after 20 min, 0.010 mL (0.039 mmol) of phosphine was added to consume the remaining alcohol. After 10 min, the mixture was washed with brine (2 mL), and the organics were dried ($MgSO_4$). The residue, after filtration and solvent removal, was purified via TLC (50% ethyl acetate/hexane, R_f 0.56) to yield 7.1 mg (69%) of allylic chloride **15**: oil; m/e, no peak match, parent; formula $C_{10}H_{15}O_1Cl_1S_1$; IR (neat, cm^{-1}) 1720 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 5.82–5.61 (2 H, m), 4.02 (2 H, d, J = 5.9 Hz), 3.33 (1 H, d, J = 13.2 Hz), 3.11–2.98 (1 H, m), 3.04 (1 H, dd, J = 13.2, 1.4 Hz), 2.53–2.31 (3 H, m), 2.31–2.00 (3 H, m), 1.67 (2 H, ddd, J = 7.4, 7.4, 7.4 Hz).

Ring Expansion of the Allylic Chloride 15 to (*Z*)- and (*E*)-11-Thiabicyclo[5.3.1]undec-3-en-10-ones 21 and 22. To a flame-dried, nitrogen-flushed round-bottom flask were added the allylic chloride **15** (7.9 mg, 0.036 mmol) in 1 mL of dry acetonitrile, sodium iodide (5.7 mg, 0.038 mmol, Mallinckrodt, gently heated under high vacuum), and a small amount of anhydrous potassium carbonate. The heterogeneous mixture was placed in a preheated oil bath (64 °C) and stirred for 90 min. The reaction mixture was cooled, diluted with ether (10 mL), and washed with brine (2 × 5 mL), and the organics were dried ($MgSO_4$). After solvent removal, the residue was eluted through a small plug of silica gel ($CHCl_3$) to yield 5.3 mg (80%) of an oil, composed of a 1.6/1 mixture of the bicyclic *Z*- and *E*-isomers **21** and **22**, respectively: analytical TLC (silica gel F254), 50% ethyl acetate/hexane, R_f 0.64; m/e, exact mass calcd for $C_{10}H_{14}O_1S_1$ 182.0762, found 182.0755, error 3.9 ppm; IR (neat, cm^{-1}) 1710 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 6.26–6.11 (0.38 H, m), 5.96 (0.62 H, ddd, J = 9.1, 9.1, 9.1 Hz), 5.50 (0.62 H, ddd, J = 9.1, 9.1, 9.1 Hz), 5.19 (0.38 H, ddd, J = 15.8 11.7, 4.5 Hz), 3.91–3.83 (0.38 H, m), 3.42–3.32 (0.62 H, m), 3.12–2.50 (4 H, m), 2.38–1.75 (7 H, m).

Horner–Emmons Reaction of Aldehyde 11. Triethyl 2-phosphonopropionate[6] (84.2 mg, 0.353 mmol) in 2 mL of dry THF was added dropwise via cannula to a stirred suspension of sodium hydride (Alfa, 50% oil dispersion, washed 3 × 5 mL THF) in 5 mL of THF. The reaction mixture was stirred for 20 min, and aldehyde **11** (65.0 mg, 0.227 mmol) in 2 mL of THF was added dropwise via cannula. After 2 h of being stirred at room temperature, the orange solution was transferred with ether (15 mL) to a separatory funnel, washed with saturated NH_4Cl (5 mL), and brine (5 mL), and the organics were dried ($MgSO_4$). After solvent removal, the residue was purified by PTLC (15% ethyl acetate/hexane, two elutions) to yield 60.1 mg (R_f 0.65, 71%) of *E*-isomer **17** along with 3.5 mg (R_f 0.75, 4%) of the *Z*-isomer. **17**: oil; m/e, exact mass calcd for $C_{19}H_{34}O_3Si_1S_1$ 370.1989, found 370.2001, error 3.2 ppm; IR (neat, cm^{-1}) 1715 (C=O), 1685 (=CO), 1660 (C=C); 200-MHz NMR ($CDCl_3$, ppm) 6.71 (1 H, br t, J = 7.4 Hz), 4.91–4.81 (1 H, m), 4.16 (2 H, q, J = 7.1 Hz), 3.21 (1 H, br d, J = 16.9 Hz), 2.86 (1 H, br d, J = 16.9 Hz), 2.78–2.64 (1 H, m), 2.46–2.01 (4 H, m), 1.83 (3 H, br s), 1.67 (2 H, ddd, J = 7.1, 7.1, 7.1 Hz), 1.26 (3 H, t, J = 7.1 Hz), 0.92 (9 H, s), 0.10 (6 H, s).

Allylic Alcohol 18. The unsaturated ester **17** (58.1 mg, 0.15 mmol) was dissolved in 3 mL of dry THF and cooled, with stirring, to 0 °C. Diisobutylaluminum hydride (Aldrich, 1.0 M in hexane, 0.36 mL, 0.36 mmol) was added dropwise and the reaction mixture stirred for 30 min. After the reaction was quenched with several drops of methanol, the mixture was diluted with ether (5 mL) and washed with saturated NH_4Cl (2 × 10 mL), water (2 × 10 mL), and brine (5 mL), and the organics were dried ($MgSO_4$). The solvent was removed, and the residue was purified via PTLC (20% ethyl acetate/hexane, R_f 0.25) to afford 32.5 mg (66%) of allylic alcohol **18**: oil; m/e, exact mass calcd for $C_{17}H_{32}O_2Si_1S_1$ 328.1884, found 328.1804, error 24.5 ppm; IR (neat, cm^{-1}) 3340 (OH), 1680 (=CO); 200-MHz NMR ($CDCl_3$, ppm) 5.36 (1 H, br t, J = 7.1 Hz), 4.97–4.86 (1 H, m), 3.96 (2 H, s), 3.21 (1 H, br d, J = 16.8 Hz), 2.84 (1 H, br d, J = 16.8 Hz), 2.78–2.61 (1 H, m), 2.50–2.30 (1 H, m), 2.25–2.02 (3 H, m), 1.68–1.53 (2 H, m), 1.65 (3 H, s), 1.65 (1 H, br s), 0.89 (9 H, s), 0.10 (6 H, s).

Keto Allylic Alcohol 19. The silyl enol ether **18** (32.5 mg, 0.099 mmol) was dissolved in 5 mL of methanol (Mallinckdrodt anhydrous) and 0.01 mL of dry THF, and 0.20 mL of triethylammonium hydrofluoride was added. The reaction mixture was stirred for 12 h at room temperature and transferred to a separatory funnel with ether (15 mL), washed with brine (7 mL), and dried ($MgSO_4$). The solvent was removed and the residue purified by flash chromatography on silica gel (50% ethyl acetate/hexane) to yield 17.0 mg (80%) of alcohol **19**: oil; analytical TLC (silica gel F254), 50% ethyl acetate/hexane, R_f 0.23; m/e, exact mass calcd for $C_{11}H_{18}O_2S_1$ 214.1023, found 214.1035, error 5.6 ppm; IR (neat, cm^{-1}) 3620 (OH), 1720 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 5.38 (1 H, br t, J = 7.1 Hz), 3.99 (2 H, s), 3.33 (1 H, d, J = 13.1 Hz), 3.10–2.97 (1 H, m), 3.08 (1 H, br d, J = 13.1 Hz), 2.50–2.38 (3 H, m), 2.23–2.01 (3 H, m), 1.70 (1 H, br s), 1.68–1.58 (2 H, m), 1.66 (3 H, s).

Allylic Chloride 20. Tri-*n*-butylphosphine (Aldrich, 0.60 mL, 0.24 mmol) was added with stirring to 3 mL of dry CCl_4. The solution was cooled to 0 °C, and alcohol **19** (30.0 mg, 0.14 mmol) in 1 mL of CCl_4 was added dropwise via cannula. The ice bath was removed after 5 min and the reaction mixture stirred for 30 min. The mixture was diluted with ether (10 mL) and washed with brine (5 mL), and the organics were dried ($MgSO_4$). The residue, after filtration and solvent removal, was purified by flash chromatography on silica gel (15% ethyl acetate/hexane) to yield 17.6 mg (54%) of allylic chloride **20**: oil; analytical TLC (silica gel F254), 20% ethyl acetate/hexane, R_f 0.33; m/e, exact mass calcd for $C_{11}H_{17}O_1Cl_1S_1$ 232.0685, found 232.0687, error 0.8 ppm; IR (neat, cm^{-1}) 1720 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 5.49 (1 H, br t, J = 6.9 Hz), 3.9 (2 H, s), 3.32 (1 H, d, J = 13.5 Hz), 3.07–3.00 (1 H, m), 3.04 (1 H, br d, J = 13.5 Hz), 2.52–2.31 (3 H, m), 2.20–2.04 (3 H, m), 1.74 (3 H, s), 1.64 (2 H, ddd, J = 7.2 and 7.2 and 7.2 Hz).

Ring Expansion of the Allylic Chloride 20 to (*Z*)-3-Methyl-11-thiabicyclo[5.3.1]undec-3-en-10-one. To a flame-dried, nitrogen-flushed round-bottom flask were added allylic chloride **20** (5.6 mg, 0.24 mmol) in 2 mL of dry acetonitrile, sodium iodide (3.9 mg, 0.026 mmol, Mallinckrodt, gently heated under high vacuum), amd ca. 50 mg of anhydrous potassium carbonate. The heterogeneous mixture was placed in a preheated oil bath (73 °C) and stirred for 1.7 h. The mixture was cooled, diluted with ether (10 mL), and washed with water (2 × 5 mL), and the organics were dried ($MgSO_4$). The solvent was removed after filtration to give a pale yellow oil that was purified by TLC (20% ethyl acetate/hexane, R_f 0.56), affording 4.4 mg (93%) of a single diastereomer determined to be the *Z*-olefin **23**: oil; m/e, exact mass calcd for $C_{11}H_{16}O_1S_1$ 196.0918, found 196.0927, error 4.6 ppm; IR ($CHCl_3$, cm^{-1}) 1705 (C=O); 270-MHz NMR ($CDCl_3$, ppm) 5.68 (1 H, br dd, J = 8.6, 8.0 Hz), 3.47–3.33 (1 H, m), 3.38 (1 H, t, J = 8.0 Hz), 2.85 (1 H, ddd, J = 16.5, 13.8, 5.7 Hz), 2.,53 (2 H, d, J = 8.0 Hz), 2.38–1.70 (7 H, m), 1.60 (3 H, s).

(*Z*)-4-Methyl-8-(methylthio)cyclodec-4-enone (25). A small spatula-tip of trimethyloxonium tetrafluoroborate (ca. 50 mg, Alfa) was placed in a flame-dried round-bottom flask equipped with a magnetic stir bar and septum. The flask was purged under a stream of nitrogen, and 2 mL of dry DME was added. The bicyclic sulfide **23** (6.4 mg, 0.033 mmol) in 0.5 mL of DME was added dropwise via cannula and the reaction stirred for 90 min (TLC, 20% ethyl acetate/hexane showed no mobile spot). A small amount of zinc dust (ca. 30 mg) and 2 drops of glacial acetic acid were added, and the reaction was stirred at room temperature for 2 h. The mixture was then diluted with ether (5 mL) and washed with saturated $NaHCO_3$ (2 mL), water (2 mL), and brine (2 mL), and the organics were dried ($MgSO_4$). The residue after solvent removal was purified by TLC (20% ethyl acetate/hexane, R_f 0.32) to afford 6.3 mg (90%) of carbocycle **25**: oil; m/e, exact mass calcd for $C_{12}H_{20}O_1S_1$ 212.123, found 212.123, error 0.1 ppm; IR ($CDCl_3$, cm^{-1}) 1720 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 5.07 (1 H, dd, J = 11.3, 4.3 Hz), 3.17 (1 H, ddd, J = 16.7, 12.1, 4.6 Hz), 2.97 (1 H, ddd, J = 11.9, 11.9, 5.5 Hz), 2.63–1.52 (11 H, m), 2.10 (3 H, br s), 1.70 (3 H, br s).

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Registry No. **6**, 80737-85-5; **7**, 80737-87-7; **8**, 83076-81-7; **9**, 109890-65-5; **10**, 109890-66-6; **11**, 109890-67-7; **12**, 109890-68-8; **13**, 109890-69-9; **14**, 109890-70-2; **15**, 109890-71-3; **16**, 3699-66-9; (*E*)-**17**, 109890-72-4; (*Z*)-**17**, 109890-79-1; **18**, 109890-73-5; **19**, 109890-74-6; **20**, 109890-75-7; **21**, 109890-76-8; **22**, 109957-49-5; **23**, 109890-77-9; **25**, 109890-78-0; 2-(*tert*-butyldimethylsiloxy)-butadiene, 80738-05-2; acetophenone, 98-86-2; 1-phenylethanol, 98-85-1; methyl (triphenylphosphoranylidene)acetate, 2605-67-6.

Stereoselective Syntheses of *cis*-2-Alkyl-6-methylpiperidines

David M. Ryckman* and Robert V. Stevens†

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

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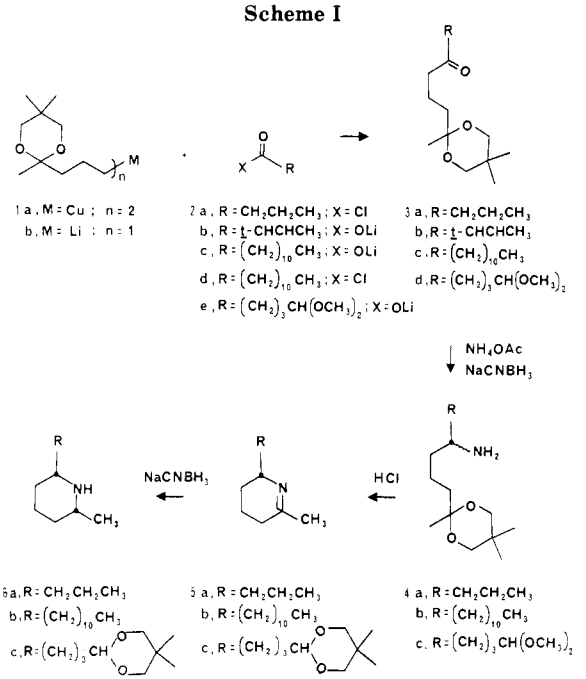
Syntheses in the pine alkaloid family, the fire ant venom series, and continued studies in the *Poranthera* species are presented. Reaction of 5-lithio-2-pentanone 2,2-dimethylpropylene ketal or the corresponding dialkylcuprate compound with carboxylic acid derivatives gives selectively protected 1,5-dicarbonyl compounds. After reductive amination of the newly formed ketone function, acidic hydrolysis of the cyclic ketal gives 6-alkyl-2-methyl-3,4,5,6-tetrahydropyridines. Stereoselective reduction of the imine function affords cis-2,6-disubstituted piperidines. Examples of this approach include syntheses of dihydropinidine from *Pinus sabiniana* and the fire ant venoms *cis*-2-methyl-6-undecylpiperidine and 2-methyl-6-undecyl-3,4,5,6-tetrahydropyridine from *Solenopis geminata* and *S. xyloni*. A preliminary report on an approach to porantherilidine, from *Poranthera corymbosa*, is described.

Introduction

Part of the research in these laboratories has been concerned with the stereochemical course of nucleophilic addition to tetrahydropyridinium ions. In the cases studied,[1] the product formed in a stereospecific manner is a substituted piperidine molecule. Previous reports from these laboratories have described a general method of synthesis of 2,3-disubstituted piperidines by the annulation of Δ^2-tetrahydropyridines, with methyl vinyl ketone.[2] The aim here is to develop methodology for the synthesis of 2,6-disubstituted piperidines. As usual, the main objectives are efficient skeletal construction and stereochemically controlled bond formations. Moreover, any general methodology should be sufficiently flexible to permit analogue development. Interest in these molecules is intense because, in addition to providing an entry to the piperidine alkaloids, the N-substituted alkyl and acyl derivatives have a broad spectrum of useful properties. Alkaloids with the 2,6-disubstituted piperidine ring structure have been detected in certain members of the pine and fire ant species. *Pinus sabiniana* yields 2,6-dimethylpiperidine, pinidine, and dihydropinidine, **6a**. Substantial amounts of pinidine have also been detected in *P. jeffreyi* and *P. torreyana*.[3] Related alkaloids have been found in other plants[4] and also in the Myrmicinae ants belonging to subgenus *Solenopsis* of the genus *Solenopsis*. Known for their particularly potent stings, the term fire ant has been given to the four main North American forms *Solenopsis*; *S. invicta* = *saevissima*, *S. richteri* = *saevissima*, *S xyloni*, and *S geminata*. The latter two types are indigenous to the southern U.S.A. The former two groups, consisting of two subspecies referred to as red and black, have been imported into this country from South America as cargo stowaways.[5]

Cyclization procedures and the reduction of pyridines are the two most widely applied methods of preparing the parent 2,6-disubstituted piperidine ring structure.[6] Several clever adaptations have been applied to the synthesis of the pine and fire ant alkaloids.[7] Herein we report our efforts directed toward the syntheses of these types of molecules. Furthermore, as part of our continued interest in general methods for the stereospecific total synthesis of natural products, preliminary results on the application

Scheme I



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