STUDIES ON THE ALKYLATION OF CHIRAL, NON-RACEMIC, TRICYCLIC PYRROLIDINONES

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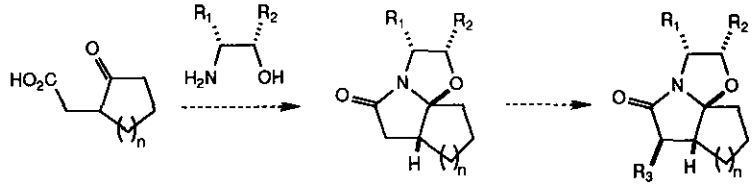
Abstract- Condensation of cyclic keto acids with chiral amino alcohols provides tricyclic pyrrolidinones with high levels of diastereoselectivity. These pyrrolidinones can be alkylated *via* their lithium or sodium enolates. Optimal alkylation conditions vary with the nature of the amino alcohol; the phenylglycinol-derived pyrrolidinones suffer from an apparent benzylic metallation, whereas the valinol and norephedrine-derived substrates are good alkylation substrates. Application of this methodology to a vinylsilane / iminium ion cyclization approach to the synthesis of Whitesell's amine was also investigated.

Introduction

Chiral pyrrolidinones have served as valuable templates for diastereoselective alkylations in a variety of synthetic applications. 4-substituted prolines[2] and pyrrolidinones,[3] 3-substituted piperidines,[4] 3,3-disubstituted pyrrolidines,[5] and a variety of carbocycles bearing quarternary chiral centers[6] have been prepared utilizing a chiral pyrrolidinone alkylation as a key step. In addition, the substrate for a propargylsilane-iminium ion cyclization leading to the *Aristotelia* alkaloid peduncularine was prepared *via* this methodology.[7]

Scheme 1



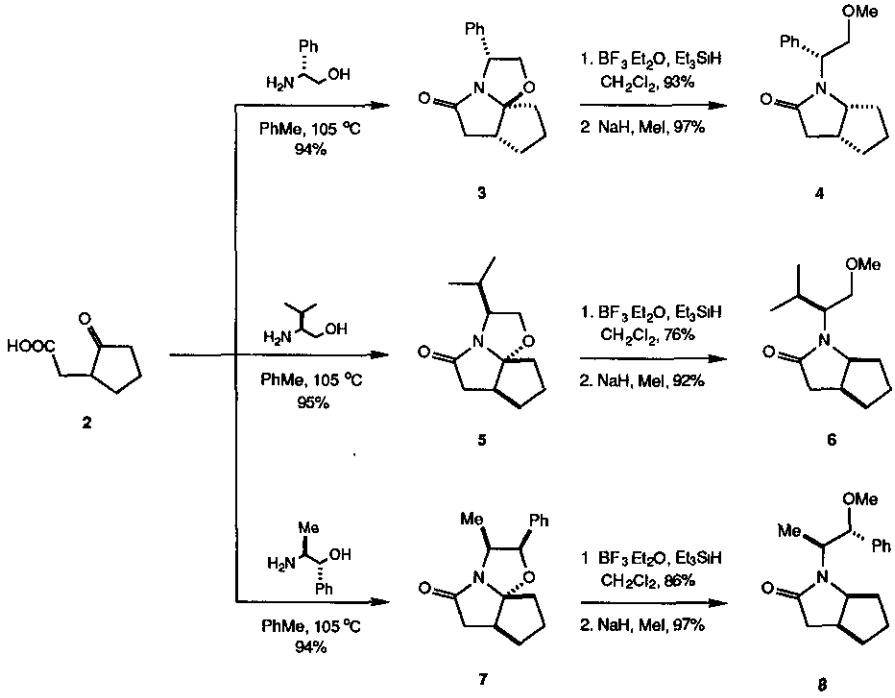
One source of chiral pyrrolidinones is the condensation of a chiral amino alcohol with a 4-keto (or aldehydo) acid.[5, 6, 8] In the course of a project directed at the synthesis of tricyclic, C_2-symmetric pyrrolidines,[9, 10] we became interested in utilizing *cyclic* keto acids in such a condensation to prepare tricyclic pyrrolidinones (Scheme 1). This paper reports our results in the preparation of these tricyclic pyrrolidinones and their subsequent alkylation.

Results and Discussion

Preparation of Alkylation Substrates

Condensation of known keto acid (**2**)[11] with *R*-(-)-phenylglycinol under conditions similar to those reported by Meyers and Burgess[8] (0.5 M in toluene, reflux, removal of water with a Dean-Stark apparatus) provided lactam (**3**) in 94% yield (Scheme 2). This reaction was highly stereoselective, with only a single diastereomer being detected in the crude reaction mixture; the initial stereochemical assignment was made in analogy to Meyers' work, and was subsequently confirmed for the norephedrine series by a single crystal X-ray analysis (*vide infra*). Keto acid (**2**) was a racemic mixture while the phenylglycinol was enantiomerically pure. Thus, formation of a single product diastereomer requires that the stereogenic center adjacent to the ketone be epimerized under the reaction conditions.

Scheme 2

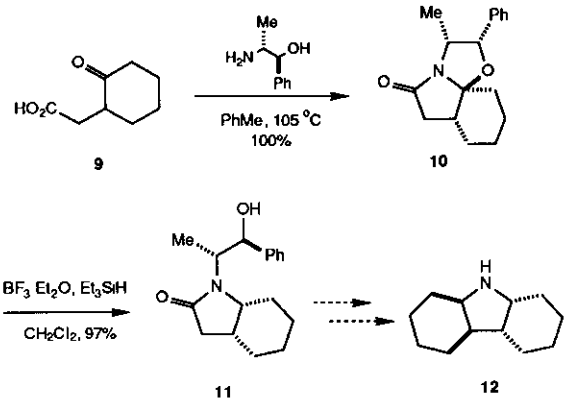


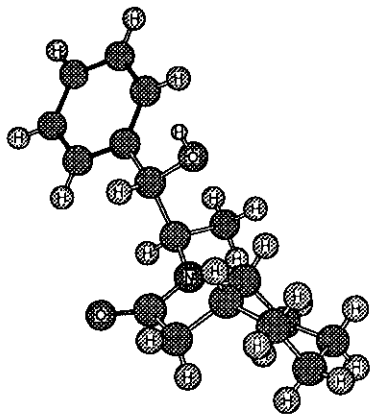
Our optimization of the pyrrolidinone alkylation required several other lactams, which were prepared as shown in Scheme 2. Condensation of (*S*)-valinol with keto acid (**2**) provided a 95% yield of a single tricyclic lactam (**5**). In similar fashion, condensation with (1*R*, 2*S*)-(-)-norephedrine provided lactam (**7**). In order to provide bicyclic pyrrolidinones for the alkylation studies, the *N,O*-acetals were reductively cleaved with $BF_3{\cdot}Et_2O$ and Et_3SiH in dichloromethane;[12] the resulting alcohols were isolated in 76-93% yields. The alcohol was then

masked as the corresponding methyl ether (NaH, MeI, THF), providing bicyclic pyrrolidinones (**4**), (**6**), and (**8**) in 92-97% yield.

The condensation of keto acid (**9**) with (1*S*, 2*R*)-norephedrine was investigated in a related project directed at the synthesis of tricyclic pyrrolidine (**12**), the 6-5-6 analog of Whitesell's amine. As shown in Scheme 3, the condensation proceeds under similar conditions to provide lactam (**10**) in quantitative yield; reductive opening of the N,O-acetal proceeded in 97% yield to provide alcohol (**11**). Crystals suitable for X-ray analysis were grown from chloroform; a Chem-3D plot of this structure is shown in Scheme 3, which supports the stereochemical assignments made earlier by analogy to Meyers' work.

Scheme 3





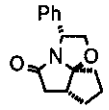
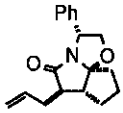
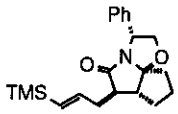
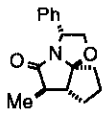
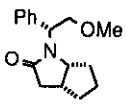
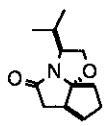
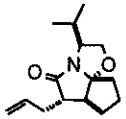
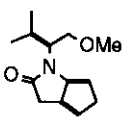
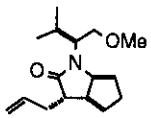
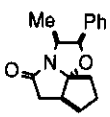
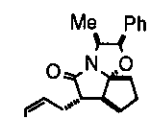
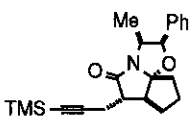
Chem-3D representation of the X-ray crystal structure of **11** .

Pyrrolidinone Alkylations

We first investigated alkylation of lactam (**3**), using LDA and MeI in THF. The reaction solution turned deep red immediately following addition of the lactam to the LDA solution; following addition of the MeI, none of the desired alkylation product could be isolated. Only the starting lactam was isolated, in poor recovery (<50%). Curious as to the failure of this seemingly straightforward reaction, we began a survey of alkylations using several different substrates and reaction conditions (see the Table).

As shown in Entries 1-5, lactam (**3**) is a poor alkylation substrate. Utilization of either alkyllithium or metal amide bases led to poor mass balances and none or very little of the desired product (Entries 1 and 5). The best conditions identified for this substrate involved overnight treatment with sodium hydride and the appropriate allylic halide in 10:1 THF-HMPA at reflux; although the isolated yields were low (34-37%), the mass balance was typically >90% (starting material could be readily separated and resubjected to the alkylation conditions).

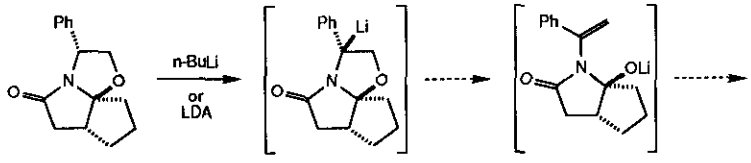
Table

Entry	Starting Material	Conditions	Product	Yield [a]
1	 **3**	n-BuLi or LDA, THF; allyl bromide		0% [b]
2		NaH, THF-HMPA; allyl bromide	 **13**	37% (70%) [c]
3		KH, THF-HMPA; allyl bromide		34% (49%) [d]
4		NaH, THF-HMPA 	 **14**	35% (44%) [e]
5		$KN(TMS)_2$; MeI, THF	 **15**	22% (37%) [b]
6	 **4**	n-BuLi or LDA, THF; allyl bromide		0% [b]
7	 **5**	n-BuLi, THF, allyl bromide	 **16**	66%
8	 **6**	LDA, THF; allyl bromide	 **17**	65%
9	 **7**	$NaN(TMS)_2$, THF; 	 **18**	55% (73%)
10		$NaN(TMS)_2$, THF; 	 **19**	34% (81%)

[a] Numbers in parentheses represent product yields based on consumed starting material.
[b] The reaction solution became deep red immediately following addition of the base.
[c] The double alkylation product was isolated in 10% yield.
[d] The double alkylation product was isolated in 19% yield.
[e] The double alkylation product was isolated in 17% yield.

Two explanations were considered for the failure of lactam (**3**) in these alkylations. The first was that the tricyclic topology of the molecule might lead to steric hindrance at the carbon α to the lactam and thus hinder enolization and/or alkylation. The second hypothesis was that the benzylic nature of the lactam nitrogen might lead to metallation of the benzylic C-H bond.[13] This intermediate might then suffer β-elimination of the oxygen atom and subsequent degradation (Scheme 4).

Scheme 4



3

The first hypothesis was ruled out by Entry 6 in the Table. Exposure of bicyclic pyrrolidinone (**4**) to either n-BuLi or LDA led to the same deep red solution observed with tricyclic lactam (**3**); none of the desired product was isolated, and the mass balance was again <50%. The second hypothesis was supported by Entries 7 and 8, in which the phenyl group of lactam (**3**) is replaced by an isopropyl group (i.e. valinol is substituted for phenylglycinol in the initial condensation). Treatment of either the tricyclic pyrrolidinone (**5**), Entry 7, or its bicyclic analog (**6**), Entry 8, led to a yellow enolate solution, in distinct contrast to the deep red color observed with lactams (**3**) or (**4**). Addition of allyl bromide then provided the desired alkylation product in 65-66% yield.

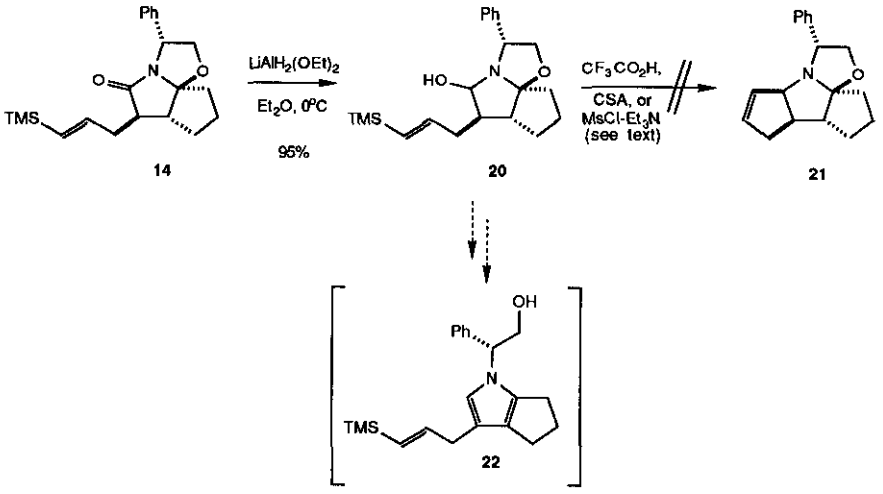
Norephedrine-derived pyrrolidinone (**7**) also proved to be a suitable alkylation substrate (Entries 9 and 10); this was investigated due to the relative costs of norephedrine ($4 per gram) and valinol ($15-20 per gram).[14] Investigation of a variety of bases for the enolization of **7** revealed $NaN(TMS)_2$ to be the optimal base (also studied were n-BuLi, LDA, $LiN(TMS)_2$, and $KN(TMS)_2$). Although the reaction typically did not proceed to completion, the mass balances were consistently high and the starting material was readily separated from the alkylation product (the reaction could be driven to completion through the use of excess base, but this invariably led to formation of the double alkylation product).

Investigation of an Iminium Ion/Vinylsilane Cyclization

The original purpose behind these pyrrolidinone alkylations was to investigate an iminium ion/vinylsilane cyclization route to Whitesell's amine (**1**).[9] We have investigated several sets of conditions for this cyclization with pyrrolidinones (**14**) and (**18**). This is shown for pyrrolidinone (**14**) in Scheme 5; similar observations were made with pyrrolidinone (**18**). Reduction of the lactam to hemi-aminal (**20**) was achieved with $LiAlH_2(OEt)_2$ in Et_2O,[15] providing a mixture of aminal diastereomers in 95% yield (the corresponding reduction of pyrrolidinone (**18**) proceeded in 98% yield). Several attempts were made to cyclize this material by exposure

to trifluoroacetic acid in acetonitrile, either at room temperature or at reflux.[16] These conditions invariably led to disappearance of the starting material and formation of a variety of products, none of which corresponded to the desired cyclization product (**21**). The intensely colored reaction mixtures as well as signals in the crude ^1H nmr suggested formation of pyrroles such as **22** and possibly susbsequent oligimerization, although no products could be isolated which would confirm this hypothesis. Similar attempts were made to cyclize the hemi-aminal derived from pyrrolidinone (**18**); again, none of the conditions investigated provided detectable amounts of the desired product. Conditions studied include CF_3CO_2H in MeCN and/or CH_2Cl_2, camphorsulfonic acid in $CHCl_3$ or MeCN, and MsCl-Et_3N in CH_2Cl_2. The latter are conditions successfully utilized by Chamberlin in a related system.[17]

Scheme 5



Conclusions and Future Work

Extension of Meyers' phenylglycinol-keto acid cyclization to cyclic keto acids provides a highly diastereoselective synthesis of tricyclic and bicyclic pyrrolidinones. While phenylglycinol-derived pyrrolidinones are poor alkylation substrates (0-37% yields), we have developed conditions for the relatively efficient alkylation of both valinol and norephedrine-derived pyrrolidinones (65-81% yields). Initial attempts to induce a vinylsilane-iminium ion cyclization on two substrates (**14** and **18**) were not successful. This reaction and its application to the preparation of Whitesell's amine (**1**) are currently under further investigation. The results of these studies will be reported in due course.

ACKNOWLEDGEMENTS

A substantial portion of the work described herein was done independently during J.A.R.'s postdoctoral fellowship in Professor Clayton Heathcock's labs at the University of California, Berkeley (6/90 through 6/92). Acknowledgement is gratefully made to the American Cancer Society for a postdoctoral fellowship during this time (Grant # PF-3547), and to Professor Heathcock for numerous helpful insights and suggestions. Mr.

Stephane Caron (University of California, Berkeley), is gratefully acknowledged for his generous assistance in the characterization of several intermediates.

EXPERIMENTAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran were distilled from sodium / benzophenone ketyl immediately prior to use. Benzene, toluene, dichloromethane, triethylamine, diisopropylethylamine, and diisopropylamine were distilled from calcium hydride prior to use. Dimethyl sulfoxide and hexamethylphosphoric triamide were distilled from CaH_2 and stored over 4-Å molecular sieves. Methyl iodide and allyl bromide were passed through a short plug of basic alumina immediately prior to use. ^{1}H-Nmr and ^{13}C- nmr spectra were recorded on Bruker AM-400 (400 MHz ^{1}H, 100 MHz ^{13}C), or Bruker AM-500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometers with deuterochloroform using residual chloroform (δ = 7.27 for ^{1}H, 77.0 for ^{13}C) as an internal reference unless otherwise stated. Infrared spectra were recorded on a Perkin-Elmer 1280 ir and were measured as thin films on NaCl plates unless otherwise noted. Peaks are reported in units of cm^{-1}. Mass spectra (ms) were measured using the chemical ionization method unless otherwise noted; data are reported as *m/z* (relative intensity). Elemental combustion analyses were performed by the University of California, Berkeley, Microanalytical Service Laboratory or Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Phenylglycinol tricyclic lactam (3). A flame-dried, 200 ml round bottom flask was charged with keto acid (**6**) (4.953 g, 34.8 mmol) and R-(-)-2-phenylglycinol (4.757 g, 34.7 mmol). 70 ml toluene was added, and the solution was warmed to reflux under nitrogen (water was collected in a Dean-Stark trap containing 4-Å molecular sieves, although several earlier, smaller scale runs suggested this might not be necessary). After 22 h the solution was cooled to room temperature and concentrated to provide a reddish brown oil. Chromatography on a 50 mm column (3:1 to 2:1 hexane-ethyl acetate) provided the desired lactam as a clear, pale yellow oil (7.897 g, 94%). Upon standing this material solidified, and was subsequently recrystallized from 5:1 hexane-ether to provide 6.02 g of a white, powdery solid in two crops. $[\alpha]_D$: -161° (*c* 2.0, CH_2Cl_2). Ir: 3060, 3030, 2970, 2880, 1710, 1605, 1495 cm^{-1}. ^{1}H Nmr (400 MHz): δ 1.55-1.85 (m, 4H), 1.92-1.98 (m, 2H), 2.49 (dd, 1H, *J* = 6.7, 17.6 Hz), 2.69-2.76 (m, 1H), 2.89 (dd, 1H, *J* = 10.5, 17.6 Hz), 3.99 (dd, 1H, *J* = 7.6, 8.6 Hz), 4.62 (t, 1H, *J* = 8.3 Hz), 5.16 (t, 1H, *J* = 7.8 Hz), 7.24-7.37 (m, 5H). ^{13}C Nmr (100 MHz): δ 24.5, 32.4, 36.7, 40.7, 41.4, 57.9, 73.5, 110.9, 125.6, 127.4, 128.7, 139.7, 180.3. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.0; N, 5.8. Found: C, 73.9; H, 7.2; N, 5.5.

Bicyclic lactam methyl ether (4). Lactam (**3**) (248 mg, 1.02 mmol) in CH_2Cl_2 (2.5 ml) was treated with Et_3SiH (0.81 ml, 5.1 mmol) and $BF_3{\cdot}Et_2O$ (1.88 ml, 15.3 mmol). The solution was stirred at room temperature for 61 h, then diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$ and brine. The aqueous phase was back extracted with three portions of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to provide 289 mg of a clear, slightly tan oil. Chromatography on a 20 mm column (1:1 to 1:2 to 1:3 to 1:5 hexane-ethyl acetate) provided the desired alcohol as a clear, colorless oil (232 mg, 93%). Ir: 3300 (br), 3040, 2970, 2880, 1660, 1610, 1500, 1450 cm^{-1}. ^{1}H Nmr (400 MHz): δ 1.46-1.73 (m, 5H), 1.78-1.88 (m, 1H), 2.24 (dd, 1H, *J* = 17.6, 4.2 Hz), 2.62-2.70 (m, 1H), 2.82 (dd, 1H, *J* = 17.6, 10.6 Hz), 3.81-3.86 (m, 1H),

3.98 (ddd, 1H, J = 12.3, 6.3, 3.5 Hz), 4.28 (dt, 1H, J = 12.3, 7.9 Hz), 4.43 (dd, 1H, J = 7.9, 3.5 Hz), 4.64 (dd, 1H, J = 7.9, 6.2 Hz), 7.25-7.37 (m, 5H). ^{13}C Nmr (100 MHz): δ 24.1, 31.9, 34.0, 34.5, 39.0, 62.8, 64.1, 64.8, 127.4, 127.8, 128.7, 137.3, 176.4.

NaH (60% by weight in oil, 63 mg, 1.6 mmol) was washed with three portions of hexane and dried under a stream of nitrogen. After cooling the flask in a 0 °C ice bath, the above alcohol (194 mg, 0.79 mmol) was added as a solution in THF *via* cannula (4 ml, rinse with 2 x 1 ml THF). Methyl iodide (197 µl, 3.2 mmol) was added, and the solution was stirred at 0 °C for 1 h and then warmed to room temperature for 1 h. The solution was diluted with Et_2O and carefully treated with aqueous NH_4Cl; the layers were separated, and the organic phase washed with brine. The aqueous phase was back extracted with two portions of Et_2O, and the organic extracts were dried over $MgSO_4$, filtered, and concentrated to provide 208 mg of a clear, orange oil. Chromatography on a 15 mm column (2:1 to 1:1 to 2:3 hexane-ethyl acetate) provided **4** as a clear, pale yellow oil (199 mg, 97%). $[\alpha]_D$: -102° (*c* 2.3, $CHCl_3$). Ir: 3060, 3020, 2950, 2870, 2820, 1675, 1480, 1450, 1410 cm^{-1}. ^{1}H Nmr (400 MHz): δ 1.35-1.55 (m, 5H), 1.74-1.82 (m, 1H), 2.18 (dd, 1H, J = 12.2, 9.4 Hz), 2.67-2.74 (m, 2H), 3.41 (s, 3H), 3.97 (dd, 1H, J = 10.1, 5.8 Hz), 4.05-4.09 (m, 1H), 4.21 (dd, 1H, J = 10.1, 8.6 Hz), 5.11 (dd, 1H, J = 8.4, 5.9 Hz), 7.25-7.39 (m, 5H). ^{13}C Nmr (100 MHz): δ 24.1, 32.5, 33.8, 34.8, 38.4, 55.4, 58.7, 63.0, 71.2, 127.6, 127.7, 128.4, 138.6, 175.5. Ms (FAB); m/z: 260 (M+1, 100). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.1; H, 8.2; N, 5.4. Found: C, 73.7; H, 8.2; N, 5.5.

Valinol tricyclic lactam (5). Keto acid (**6**)(2.484 g, 17.5 mmol) and S-(+)-valinol (1.802 g, 17.5 mmol) were dissolved in toluene (35 ml) and heated to reflux under nitrogen (water was collected in a Dean-Stark trap containing 4-Å molecular sieves). After 21 h the solution was cooled to room temperature and concentrated to provide a clear, orange oil. Chromatography on a 30 mm column (5:1 to 3:1 hexane-ethyl acetate) provided the desired lactam as a clear, pale yellow oil (3.465 g, 95%). $[\alpha]_D$: +76° (*c* 4.6, $CHCl_3$). Ir: 2980, 2870, 1715, 1465, 1350 cm^{-1}. ^{1}H Nmr (500 MHz): δ 0.87 (d, 3H, J = 6.6 Hz), 1.02 (d, 3H, J = 6.6 Hz), 1.44-1.50 (m, 1H), 1.58-1.66 (m, 1H), 1.68-1.81 (m, 3H), 1.84-1.90 (m, 1H), 1.95-2.01 (m, 1H), 2.35 (dd, 1H, J = 6.8, 17.6 Hz), 2.55-2.61 (m, 1H), 2.75 (dd, 1H, J = 10.5, 17.6 Hz), 3.60 (dt, 1H, J = 10.3, 7.0 Hz), 3.71 (dd, 1H, J = 6.7, 8.6 Hz), 4.15 (dd, 1H, J = 7.4, 8.5 Hz). ^{13}C Nmr (125 MHz): δ 18.8, 20.5, 24.7, 32.4, 33.0, 37.4, 40.4, 41.5, 61.6, 71.3, 110.2, 180.1. HRMS calcd for $C_{12}H_{19}NO_2$ (M+): 209.1416, found 209.1416.

Bicyclic lactam methyl ether (6). Lactam (**5**) (591 mg, 2.82 mmol) in 7.6 ml CH_2Cl_2 was treated with Et_3SiH (2.3 ml, 14 mmol) and $BF_3{\cdot}Et_2O$ (5.2 ml, 42 mmol); the solution was then warmed to reflux in a 65 °C oil bath for 15 h. After cooling to room temperature, the solution was added slowly to a vigorously stirring solution of ice-cold, aqueous $NaHCO_3$; the aqueous phase was adjusted to pH 6 by the addition of 15% aqueous NaOH. The layers were then separated, the organics washed with brine, and the aqueous phase back extracted with two portions of CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated to provide 539 mg of a clear, colorless oil. Chromatography on a 20 mm column (1:1 to 1:2 to 1:3 to 1:5 hexane-ethyl acetate) provided the desired alcohol as a clear, colorless oil (453 mg, 76%). Ir: 3500-3200 (br), 2980, 2870, 1655, 1450, 1420 cm^{-1}. ^{1}H Nmr (500 MHz): δ 0.93 (d, 3H), 1.02 (d, 3H), 1.49-1.53 (m, 1H), 1.61-1.65 (m, 3H), 1.69-1.74 (m, 1H), 1.78-1.83 (m, 1H), 2.10-2.17 (m, 1H), 2.61-2.79 (m, 4H), 3.71 (d, 1H), 3.92-3.98 (m, 1H),

4.03-4.06 (m, 1H), 5.12 (d, 1H). ^{13}C Nmr (125 MHz): δ 19.8, 20.4, 23.6, 25.8, 32.2, 34.4, 34.7, 38.7, 64.2, 65.3, 68.4, 176.6.

NaH (60% by weight in oil, 168 mg, 4.1 mmol) was washed with three portions of hexane and dried under a stream of nitrogen. After cooling the flask in a 0 °C ice bath, the above alcohol (432 mg, 2.04 mmol) was added as a solution in THF *via* cannula (8 ml, rinse with 2 x 2 ml THF). Methyl iodide (510 µl, 8.2 mmol) was added, and the solution was stirred at 0 °C for 30 min and then warmed to room temperature for 2 h. The solution was diluted with Et_2O and carefully treated with aqueous NH_4Cl; the layers were separated, and the organic phase was washed with 5% aqueous $Na_2S_2O_3$ and brine. The aqueous phase was back extracted with two portions of Et_2O, and the organic extracts were dried over $MgSO_4$, filtered, and concentrated to provide 499 mg of a clear, orange oil. Chromatography on a 20 mm column (3:1 to 2:1 to 1:1 hexane-ethyl acetate) provided **6** as a clear, pale yellow oil (425 mg, 92%). $[\alpha]_D$: +30° (*c* 5.8, $CHCl_3$). Ir: 2930, 2860, 2810, 1675, 1460, 1445, 1435, 1410 cm^{-1}. ^{1}H Nmr (400 MHz): δ 0.90 (d, 3H, *J* = 6.7 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 1.40-1.47 (m, 1H), 1.53-1.71 (m, 3H), 1.76-1.85 (m, 2H), 2.03-2.17 (m, 2H), 2.60-2.72 (m, 2H), 3.29 (s, 3H), 3.41-3.46 (m, 1H), 3.52 (dd, 1H, *J* = 3.7, 10.3 Hz), 3.76 (dd, 1H, *J* = 8.4, 10.3 Hz), 4.01-4.04 (m, 1H). ^{13}C Nmr (100 MHz): δ 20.3, 20.4, 24.4, 28.6, 32.8, 34.0, 34.8, 38.6, 58.6, 60.1, 64.8, 71.4, 175.5. HRMS calcd for $C_{13}H_{23}NO_2$ (M+): 225.1729, found 225.1737.

Norephedrine tricyclic lactam (7). Keto acid (**2**) (1.388 g, 9.76 mmol) and (1*R*, 2*S*)-norephedrine (1.480 g, 9.79 mmol) were dissolved in toluene (20 ml) and heated to reflux under nitrogen (water was collected in a Dean-Stark trap containing 4-Å molecular sieves). After 22 h the solution was cooled to room temperature and concentrated to provide a clear, orange oil. Chromatography on a 40 mm column (5:1 to 3:1 hexane-ethyl acetate) provided the desired lactam as a clear, pale yellow oil (2.356 g, 94%) which solidified upon standing to an oily white solid. $[\alpha]_D$: -17° (*c* 1.2, $CHCl_3$). Ir: 2980, 2870, 1710, 1450 cm^{-1}. ^{1}H Nmr (400 MHz): δ 0.76 (d, 3H, *J* = 7.2 Hz), 1.54-1.58 (m, 1H), 1.67-1.70 (m, 1H), 1.82-1.91 (m, 2H), 2.04-2.08 (m, 2H), 2.28-2.33 (m, 1H), 2.63-2.71 (m, 2H), 4.47 (m, 1H), 4.82 (d, 1H, *J* = 5.5 Hz), 7.19-7.30 (m, 5H). ^{13}C Nmr (100 MHz): δ 13.9, 24.0, 31.0, 39.3, 40.3, 44.8, 55.3, 82.1, 109.3, 125.9, 127.6, 128.1, 136.6, 179.2. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.7; H, 7.4; N, 5.4. Found: C, 74.4; H, 7.6; N, 5.3.

Allylated lactam (13). NaH (60% by weight in oil, 70 mg, 1.8 mmol) was washed with three portions of hexane and dried under a stream of nitrogen. Lactam (**3**) (110 mg, 0.452 mmol) was then added, followed by THF (3 ml), HMPA (0.30 ml), and allyl bromide (235 µl, 2.72 mmol). The resulting slurry was warmed to reflux for 21 h, then cooled to room temperature and treated with an additional portion of allyl bromide (235 µl, 2.72 mmol). After warming to reflux for another 13 h, the solution was cooled to room temperature and partitioned between Et_2O and aqueous NH_4Cl. The organic phase was separated, washed with brine, and the aqueous phase was extracted with an additional portion of Et_2O. The organics were dried over $MgSO_4$, filtered, and concentrated to provide 160 mg of a clear, yellow oil. Chromatography on a 15 mm column (20:1 to 10:1 hexane-ethyl acetate) provided the bis-alkylation product as a clear, colorless oil (14.8 mg, 10%). $[\alpha]_D$: -142° (*c* 3.0, $CHCl_3$). Ir: 3070, 2970, 2880, 1710, 1640, 1600, 1490, 1450, 1440 cm^{-1}. ^{1}H Nmr (400 MHz): δ 1.71-1.88 (m, 6H), 2.27-2.32 (m, 1H), 2.39-2.44 (m, 3H), 2.66-2.69 (m, 1H), 3.91 (dd, 1H, *J* = 8.6, 7.7 Hz), 4.57 (t, 1H, *J* = 8.4 Hz), 5.10-5.17 (m, 5H), 5.68-5.75 (m, 1H), 5.91-5.98 (m, 1H), 7.23-7.36 (m, 5H). ^{13}C Nmr

(100 MHz): δ 25.8, 26.3, 36.4, 38.7, 41.9, 50.5, 52.4, 58.2, 72.8, 108.20, 118.2, 118.8, 125.7, 127.3, 128.6, 133.5, 133.9, 140.1, 184.1. Ms (FAB); m/z: 284 (M+1, 100). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 78.0; H, 7.8; N, 4.3. Found: C, 77.6; H, 8.0; N, 4.1.

Second to elute was the desired product (**13**) as a clear, colorless oil (47.7 mg, 37%). Ir: 3070, 3030, 2960, 2880, 1715, 1645, 1500, 1455 cm^{-1}. ^1H Nmr (400 MHz): δ 1.55-1.59 (m, 1H), 1.68-1.84 (m, 3H), 1.90-2.01 (m, 2H), 2.23-2.29 (m, 1H), 2.42-2.46 (m, 1H), 2.59-2.69 (m, 2H), 3.97 (dd, 1H, *J* = 8.6, 7.5 Hz), 4.57 (t, 1H, *J* = 8.3 Hz), 5.07-5.17 (m, 3H), 5.73-5.82 (m, 1H), 7.25-7.36 (m, 5H). ^{13}C Nmr (100 MHz): δ 24.9, 31.8, 35.5, 36.7, 48.4, 51.3, 57.8, 73.1, 108.6, 117.3, 125.7, 127.4, 128.7, 135.3, 139.7, 180.9. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.5; N, 4.9. Found: C, 76.6; H, 7.7; N, 4.6

Further elution with 5:1 to 3:1 to 2:1 hexane-ethyl acetate provided recovered starting material as a clear, pale yellow oil (52.0 mg, 47%).

***E*-Vinylsilane lactam (14)**. NaH (60% by weight in oil, 0.42 g, 11 mmol) was washed with three portions of hexane and dried under a stream of nitrogen. Lactam (**3**) (575 mg, 2.36 mmol) was then added, followed by THF (16 ml), HMPA (1.6 ml), and *E*-3-trimethylsilyl-2-propenylbromide (910 mg, 4.71 mmol). The resulting slurry was warmed to reflux for 21 h, then cooled to room temperature, diluted with 20 ml Et_2O, and carefully quenched with 20 ml aqueous NH_4Cl. The layers were separated, and the organic phase was washed with brine. The aqueous phase was back extracted with two portions of Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to provide 1.332 g of a clear, orange oil. Chromatography on a 30 mm column (20:1 to 15:1 to 10:1 hexane-ethyl acetate) provided the bis-alkylation product as a clear, bright yellow oil (188 mg, 17%). ^1H Nmr (400 MHz): δ 1.72-1.85 (m, 6H), 2.33-2.49 (m, 4H), 2.66-2.71 (m, 1H), 3.91 (t, 1H), 4.57 (t, 1H), 5.15 (t, 1H), 5.73-5.81 (m, 2H), 5.88-5.94 (m, 1H), 6.08-6.18 (m, 1H), 7.24-7.38 (m, 5H).

Second to elute was the desired product (**14**) as a clear, pale yellow oil (295 mg, 35%). $[\alpha]_D$: -115° (*c* 2.2, $CHCl_3$). Ir: 3070, 3030, 2960, 2880, 1715, 1620 cm^{-1}. ^1H Nmr (400 MHz): δ 0.06 (s, 9H), 1.53-1.56 (m, 1H), 1.69-1.80 (m, 3H), 1.90-1.99 (m, 2H), 2.22-2.30 (m, 1H), 2.41-2.44 (m, 1H), 2.60-2.66 (m, 1H), 2.73-2.78 (m, 1H), 3.97 (t, 1H, *J* = 8.0 Hz), 4.55 (t, 1H, *J* = 7.9 Hz), 5.15 (t, 1H, *J* = 7.6 Hz), 5.77 (d, 1H, *J* = 19.5 Hz), 5.97 (dt, 1H, *J* = 18.6, 6.5 Hz), 7.25-7.36 (m, 5H). ^{13}C Nmr (100 MHz): δ -1.3, 24.9, 31.8, 36.7, 38.5, 48.5, 51.25, 57.8, 73.1, 108.6, 125.7, 127.4, 128.7, 133.5, 139.7, 143.4, 181.0. Ms (FAB); m/z: 356 (M+1, 100). Anal. Calcd for $C_{21}H_{29}NO_2Si$: C, 70.9; H, 8.2; N, 3.9. Found: C, 70.9; H, 8.4; N, 3.7.

Further elution with 5:1 to 3:1 to 2:1 hexane-ethyl acetate provided recovered starting material as a clear, pale yellow oil (117 mg, 20%).

Allylated lactam (16). To a solution of iPr_2NH (80 µl, 0.56 mmol) in THF (1 ml) at 0 °C was added butyllithium (0.31 ml of a 1.69 M solution in hexanes, 0.52 mmol). The resulting solution was stirred at 0 °C for 15 min, then cooled to -78 °C. Lactam (**5**) (97.1 mg, 0.431 mmol) was added as a solution in THF *via* cannula (2 x 1 ml). After 30 min, allyl bromide (186 µl, 2.2 mmol) was added, and the solution was stirred at -78 °C for 10 min, then at 0 °C to room temperature overnight. After 18 h, the solution was partitioned

between aqueous NH_4Cl and Et_2O, the layers were separated, and the organic phase was washed with brine. The aqueous phase was back extracted with two portions of Et_2O, and the organic extracts were dried over $MgSO_4$. Filtration and concentration provided 97.2 mg of a clear, pale yellow oil, which was purified by chromatography on an 8 mm column (5:1 to 3:1 hexane-ethyl acetate) to provide the desired product as a clear, pale yellow oil (73.8 mg, 65%). $[\alpha]_D$: +57° (*c* 2.9, $CHCl_3$). Ir: 2970, 2880, 1680, 1640, 1470, 1445, 1420 cm^{-1}. ^1H Nmr (400 MHz): δ 0.89 (d, 3H, *J* = 6.7 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 1.42-1.48 (m, 1H), 1.51-1.62 (m, 3H), 1.73-1.80 (m, 2H), 2.02-2.10 (m, 1H), 2.12-2.22 (m, 2H), 2.37-2.42 (m, 1H), 2.51-2.54 (m, 1H), 3.27 (s, 3H), 3.40-3.43 (m, 1H), 3.49 (dd, 1H, *J* = 3.8, 10.3 Hz), 3.76 (dd, 1H, *J* = 8.5, 10.3 Hz), 3.90-3.92 (m, 1H), 5.00-5.09 (m, 2H), 5.72-5.79 (m, 1H). ^{13}C Nmr (100 MHz): δ 20.26, 20.28, 24.6, 286, 32.7, 33.4, 36.5, 41.0, 49.1, 58.5, 60.0, 62.9, 71.1, 116.7, 135.9, 176.7. HRMS calcd for $C_{15}H_{23}NO_2$ (M+): 249.1729, found 249.1725.

Allylated bicyclic valinol lactam (17). To a solution of iPr_2NH (80 µl, 0.56 mmol) in THF (1 ml) at 0 °C was added butyllithium (0.31 ml of a 1.69 M solution in hexanes, 0.52 mmol). The resulting solution was stirred at 0 °C for 15 min, then cooled to -78 °C. Lactam (**6**) (97.1 mg, 0.431 mmol) was added as a solution in THF *via* cannula (2 x 1 ml). After 30 min, allyl bromide (186 µl, 2.2 mmol) was added, and the solution was stirred at -78 °C for 10 min, then at 0 °C to room temperature overnight. After 18 h, the solution was partitioned between aqueous NH_4Cl and Et_2O, the layers were separated, and the organic phase was washed with brine. The aqueous phase was back extracted with two portions of Et_2O, and the organic extracts were dried over $MgSO_4$. Filtration and concentration provided 97.2 mg of a clear, pale yellow oil, which was purified by chromatography on an 8 mm column (5:1 to 3:1 hexane-ethyl acetate) to provide the desired product as a clear, pale yellow oil (73.8 mg, 65%). $[\alpha]_D$: +29° (*c* 2.4, $CHCl_3$). Ir: 2970, 2880, 1680, 1640, 1470, 1445, 1420 cm^{-1}. ^1H Nmr (400 MHz): δ 0.89 (d, 3H, *J* = 6.7 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 1.42-1.48 (m, 1H), 1.51-1.62 (m, 3H), 1.73-1.80 (m, 2H), 2.02-2.10 (m, 1H), 2.12-2.22 (m, 2H), 2.37-2.42 (m, 1H), 2.51-2.54 (m, 1H), 3.27 (s, 3H), 3.40-3.43 (m, 1H), 3.49 (dd, 1H, *J* = 3.8, 10.3 Hz), 3.76 (dd, 1H, *J* = 8.5, 10.3 Hz), 3.90-3.92 (m, 1H), 5.00-5.09 (m, 2H), 5.72-5.79 (m, 1H). ^{13}C Nmr (100 MHz): δ 20.26, 20.28, 24.6, 28.6, 32.7, 33.4, 36.5, 41.0, 49.1, 58.5, 60.0, 62.9, 71.1, 116.7, 135.9, 176.7. HRMS calcd for $C_{16}H_{27}NO_2$ (M+): 265.2042, found 265.2027.

***Z*-Vinylsilane lactam (18).** Lactam (**7**) (473 mg, 1.84 mmol) was dissolved in 3 ml THF and cooled to -78 °C under nitrogen. $NaN(TMS)_2$ (3.7 ml of a 1.0 M solution in THF, 3.7 mmol) was added dropwise; after 50 min, *Z*-3-trimethylsilyl-2-propenyl bromide (781 mg, 4.04 mmol) was added in 1 ml THF. The solution was stirred at -78 °C for 2 h, then at 0 °C for 3 h. The reaction was quenched with aqueous $NaHCO_3$, then diluted with EtOAc. The layers were separated, and the organic phase washed with brine. The aqueous phase was back extracted with two portions of EtOAc, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to provide 799 mg of a clear, pale yellow oil. Chromatography on a 40 mm column (8:1 to 7:1 to 5:1 to 3:1 hexane-ethyl acetate) provided the desired product as a clear, pale yellow oil (227 mg, 34%): $[\alpha]_D$: +44° (*c* 2.9, $CHCl_3$). Ir ($CHCl_3$ solution): 3029, 3009, 2959, 2875, 1699, 1604, 1451, 1363, 1250 cm^{-1}. ^1H Nmr (300 MHz): δ 0.13 (s, 9H), 0.83 (d, 3H, *J* = 7.1 Hz), 1.66-1.81 (m, 2H), 1.85-2.02 (m, 2H), 2.04-2.17 (m, 2H), 2.35-2.75 (m, 4H), 4.50-4.57 (m, 1H), 4.80 (d, 1H, *J* = 5.4 Hz), 5.63 (d, 1H, *J* = 12.8 Hz), 6.21-6.32 (m,

1H), 7.28-7.42 (m, 5H). ^{13}C Nmr (75 MHz): δ 0.2, 14.0, 24.6, 30.8, 34.0, 40.3, 49.4, 51.2, 55.5, 82.3, 107.3, 126.1, 127.8, 128.3, 132.1, 136.7, 144.7, 180.2. Ms (CI); m/z: 370 (M+1, 100). HRMS calcd for $C_{22}H_{31}NO_2Si$ (M+): 367.1968, found 367.1962.

Second to elute was the starting lactam as a pale yellow oil (273 mg, 58%).

TMS acetylene lactam (19). Lactam (**7**) (1.417 g, 5.51 mmol) was dissolved in 25 ml THF and cooled to -78 °C under nitrogen. $NaN(TMS)_2$ (11 ml of a 1.0 M solution in THF, 11 mmol) was added dropwise; after 90 min, 3-trimethylsilyl-2-propynyl bromide (3.157 g, 16.5 mmol) was added in 2 ml THF. The solution was stirred at -78 °C for 2 h, then warmed slowly to room temperature over 16 h. The reaction was quenched with aqueous $NaHCO_3$, then diluted with EtOAc. The layers were separated, and the aqueous phase was extracted once with EtOAc. The organic phase was washed twice with 5% $Na_2S_2O_3$, once with brine, then dried over $MgSO_4$, filtered, and concentrated to provide 3.397 g of a dark, orange-brown oil. Chromatography on a 50 mm column (9:1 to 8:1 to 5:1 to 2:1 hexane-ethyl acetate) provided the desired product as a clear, pale yellow oil (1.104 g, 55%). $[\alpha]_D$: +64° (*c* 1.1, $CHCl_3$). Ir ($CHCl_3$ solution): 3018, 3009, 2963, 2875, 2176, 1703, 1452, 1366, 1252 cm^{-1}. ^1H Nmr (300 MHz): δ 0.10 (s, 9H), 0.80 (d, 3H, *J* = 7.1 Hz), 1.60-1.81 (m, 2H), 1.84-2.21 (m, 4H), 2.32-2.88 (m, 4H), 4.47-4.58 (m, 1H), 4.83 (d, 1H, *J* = 5.4 Hz), 7.26-7.48 (m, 5H). ^{13}C Nmr (75 MHz): δ 0.03, 13.9, 21.0, 24.6, 30.7, 40.3, 48.3, 51.1, 55.8, 82.5, 87.0, 103.6, 107.3, 126.0, 127.7, 128.3, 136.6, 179.2. Ms (CI); m/z: 368 (M+1, 100). HRMS calcd for $C_{22}H_{31}NO_2Si$ (M+): 369.2124, found 369.2118.

Second to elute was the starting lactam as a pale yellow oil (361 mg, 25%).

***E* -Vinylsilane-hemiaminal (20).** To a solution of lactam (**14**) (101 mg, 0.283 mmol) in 2 ml Et_2O at 0 °C was added $LiAlH_2(OEt)_2$ (236 µl of a 0.90 M solution in Et_2O, 0.21 mmol, prepared as described below). After stirring at 0 °C for 3.5 h, the solution was treated with 8 µl H_2O, 8 µl 15% NaOH, and 25 µl H_2O (Fieser work-up). The solution was then dried over Na_2SO_4, filtered, and concentrated to provide 103 mg of a clear, colorless oil; ^1H and ^{13}C nmr showed a small amount of starting lactam plus signals consistent with the desired hemi-aminal as a mixture of anomers. This material was subjected to cyclization conditions (CF_3CO_2H in MeCN, see text) without further purification. Ir: 3550-3300 (br), 2960, 2880, 1715, 1615, 1490, 1450 cm^{-1}. ^1H Nmr (400 MHz): (peaks listed for the major isomer only) δ 0.06 (s, 9H), 1.40-1.60 (m, 2H), 1.69-1.88 (m, 5H), 2.15-2.24 (m, 2H), 2.50-2.58 (m, 1H), 3.77-3.81 (m, 1H), 4.23-4.28 (m, 1H), 4.34-4.40 (m, 2H), 5.73 (d, 1H, *J* = 18.4 Hz), 6.05 (dt, 1H, *J* = 18.5, 6.8 Hz), 7.22-7.40 (m, 5H). ^{13}C Nmr (100 MHz): (peaks listed for the major isomer only) δ -1.2, 25.1, 30.8, 38.4, 39.4, 50.4, 54.1, 67.1, 72.2, 98.0, 112.6, 126.4, 127.0, 128.4, 132.3, 142.5, 144.6. Anal. Calcd for $C_{21}H_{31}NO_2Si$: C, 70.5; H, 8.7; N, 3.9. Found: C, 70.6; H, 8.4; N, 3.6.

Preparation of $LiAlH_2(OEt)_2$: 1.0 ml of $LiAlH_4$ (1.0 M in THF) was cooled to 0 °C under nitrogen. Ethyl acetate (98 µl, 1.0 mmol) was added dropwise, and the solution was stirred for 40 min prior to use in the above reduction. The concentration was assumed to be 0.90 M (1.0 mmol in 1.1 ml total volume).

Z-vinylsilane-hemiaminal derived from pyrrolidinone (18). To a solution of lactam (**18**) (306 mg, 0.828 mmol) in 7 ml THF at 0 °C was added $LiAlH_2(OEt)_2$ (1.80 ml of a 0.90 M solution in THF, 1.66 mmol, prepared as described above). After stirring at 0 °C for 4.5 h, tlc analysis indicated some remaining starting material; an additional 0.46 ml of $LiAlH_2(OEt)_2$ solution (0.41 mmol) was added, and the solution stirred for another 2 h. The reaction was quenched by the addition of 81 µl H_2O, 81 µl 15% NaOH, and 244 µl H_2O. The solution was then dried over Na_2SO_4, filtered, and concentrated to provide 302 mg (0.813 mmol, 98%) of the hemi-aminal as a clear, colorless oil. This material could be further purified by flash chromatography (7:1 hexane-EtOAc), but chromatographed material was essentially identical with the crude product by nmr analysis. ^{1}H Nmr (300 MHz): δ 0.11 (s, 9H), 0.74 (d, 3H, J = 7.1 Hz), 1.47-1.60 (m, 2H), 1.63-1.88 (m, 2H), 1.95-2.06 (m, 2H), 2.08-2.18 (m, 1H), 2.21-2.36 (m, 1H), 2.38-2.57 (m, 2H), 3.49-3.60 (m, 1H), 4.26 (br t, 1H), 4.91 (d, 1H, J = 5.4 Hz), 5.56 (d, 1H, J = 12.8 Hz), 6.32-6.45 (m, 1H), 7.19-7.38 (m, 5H). ^{13}C Nmr (75 MHz): δ 0.3, 16.0, 24.8, 29.9, 34.9, 40.9, 51.3, 52.2, 61.3, 78.8, 94.5, 110.5, 126.0, 127.1, 128.2, 130.6, 138.1, 145.9. Ms (CI); m/z: 372 (M+1, 38), 354 (-H_2O, 100). Anal. Calcd for $C_{22}H_{33}NO_2Si$: C, 71.1; H, 9.0; N, 3.8. Found: C, 71.0; H, 9.0; N, 3.4.

X-Ray Crystallographic Analysis of 11. The reflection data were collected at room temperature on a Siemens R3RA/v diffractometer. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[18] All crystallographic calculations were facilitated by the SHELXTL system.[19]

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogen on oxygen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 4.33%. A final difference Fourier revealed no missing or misplaced electron density.

Crystal data for pyrrolidinone (**11**): Chemical formula, $C_{17}H_{23}NO_2$; Formula weight, 273.4; Space group, $P2_12_12_1$; Cell dimensions (Å): a = 8.826(2), b = 12.826(3), c = 13.443(3); Crystal size (mm): 0.24 x 0.25 x 0.34.

REFERENCES AND NOTES

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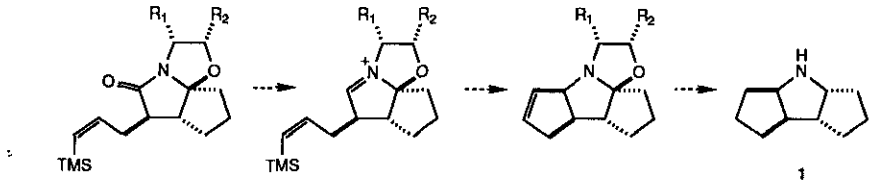

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