Asymmetric Synthesis of (−)-Trichodiene. Generation of Vicinal Stereogenic Quaternary Centers via the Thio-Claisen Rearrangement

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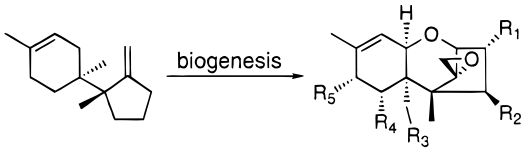
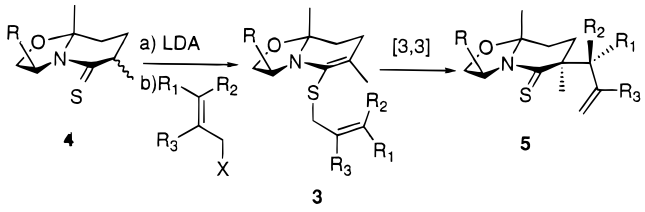
Abstract: The use of chiral bicyclic lactams, in their thiocarbonyl form **9**, has been shown to serve as important intermediates for producing α-quaternary alkyl derivatives **8**, which were readily transformed into the title compound (−)-**1**. The reversibility of the thio-Claisen rearrangement, **15**⇌**8**, was clearly demonstrated and appears to be unprecedented. Solvent effects to alter the equilibrium position were studied and found to have only a moderate, but beneficial effect. The title compound was obtained in 14% overall yield in 10 steps from bicyclic lactam, **9**.

The sesquiterpene trichodiene, (+)-**1**, isolated from the fermentation broth of the mycelium of *Tricothecium roseum*,[1] is the postulated biogenetic precursor[2] to the trichothecene mycotoxins **2** which are fungal metabolites from the *Fusarium* species.[3] The trichothecene mycotoxins have been shown to exhibit diverse biological activities.[4] The biosynthesis of trichodiene has been suggested to occur via cyclization of farnesyl pyrophosphate mediated by trichodiene synthetase,[5] an enzyme isolated from the fungus *T. roseum*. Trichodiene, although devoid of heteroatoms, presents an interesting challenge to the synthetic chemist owing to the two vicinal stereogenic quaternary carbons. Since its isolation, several racemic syntheses have appeared in the literature,[6] and one report described the preparation of the sesquiterpene in enantiomerically enriched form (47% ee).[6a] To date, this sesquiterpene has eluded any effort toward an asymmetric total synthesis. We report herein the results of our efforts which culminated with the asymmetric total synthesis of (−)-trichodiene (**1**).



We recently described the [3,3]-sigmatropic rearrangement of the *S*-alkylthioenamine **3**, derived from *S*-alkylation of a chiral nonracemic bicyclic thiolactam **4** with various allylic halides. This resulted in the formation of compounds (e.g., **5**) bearing



vicinal quaternary centers or stereogenic quaternary-tertiary centers.[7] The further development of this potentially useful synthetic method, e.g., transposing a C−S single bond for a C−C single bond,[8] had set the stage to synthesize more complex

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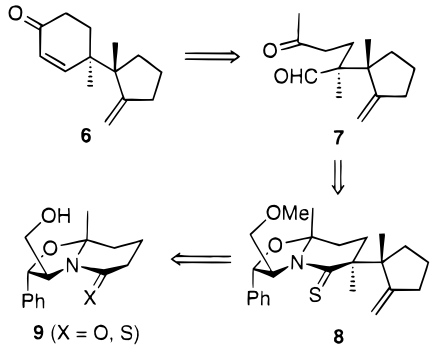
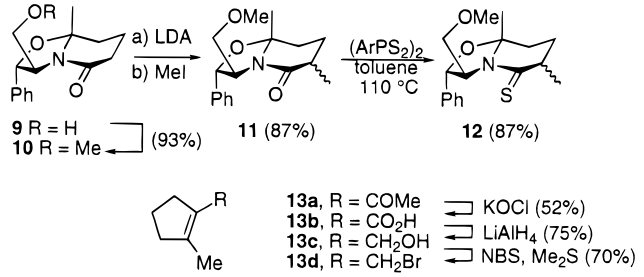
systems, such as carbon frameworks bearing vicinal stereogenic quaternary centers found in trichodiene. We envisaged that (−)-trichodiene (**1**) would be accessible from the chiral enone **6**, obtained in enantiomerically pure form, via a route similar to that described by Pearson[6d] for *rac*-**1**. The nonracemic enone **6**, in turn, would be derived from the keto-aldehyde **7** obtained from hydrolysis of thiolactam **8** via a previously described sequence.[7] The cornerstone of the synthesis relied on the successful preparation of thiolactam **8**, which was anticipated to arise via a diastereoselective [3,3]-sigmatropic rearrangement of the *S*-alkylthioenamine (e.g., **3**, or **15**) derived from *S*-alkylation of the thiolactam **9** (X = S). This rearrangement



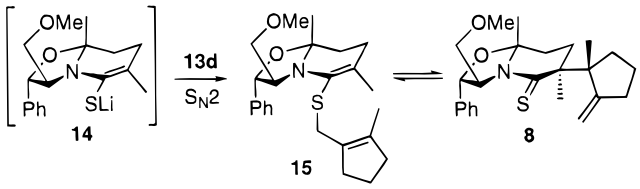
would simultaneously establish the required relative and absolute stereochemistry for the adjacent quaternary centers.[9]

The readily available, enantiomerically pure, chiral bicyclic lactam **9** (X = O)[10] was transformed into the corresponding methyl ether **10** (93%)[11] which was converted into its enolate and alkylated to produce the monomethyl derivative **11** as a 1.2:1 mixture of epimers in 87% yield. This mixture was of no consequence since this newly introduced stereogenic center would be rendered planar during a subsequent thioenolate formation (vide infra). Treatment of bicyclic lactam **11** with the Belleau reagent[12] in refluxing toluene smoothly thionated the carbonyl group to furnish the corresponding thiolactam **12**, as the same 2:1 mixture of epimers, in 87% yield. The requisite allylic bromide **13d** was readily prepared from a known[13]



cyclopentene precursor in four steps. Thus, direct acetylation of cyclohexane provided the unsaturated ketone **13a** (41%) which was then oxidized (KOCl) to the corresponding carboxylic acid **13b** (52%). Reduction of the carboxylic acid with $LiAlH_4$ provided the known allylic alcohol **13c**[14] (75%) which was subsequently transformed, using NBS-Me_2S, into the highly unstable allylic bromide **13d**.[15] Even though **13d** could be isolated in good yield (70%), it was generally stored for 1−2 h at −20 °C until ready for use in the *S*-alkylation of the bicyclic thiolactam **12**.

Treatment of **12** with LDA (1.2 equiv, THF, 0 °C), to generate the thioenolate **14**, followed by addition of the allylic bromide **13d** (1.2 equiv) resulted in the smooth formation of the crude *S*-alkylthioenamine **15**, contaminated, however, by halide **13d**. This was demonstrated by inspection of the ^{1}H NMR spectrum of the crude product which unequivocally showed that (a) alkylation had occurred *exclusively* at sulfur and (b) that thiophilic attack of the anion **14**, derived from **12**, occurred only in a S_N2 fashion with no S_N2' product being visible. The formation of the *S*-alkylated thioenamine **15** augered well for the original synthetic route that the key thiolactam **8** could indeed arise via a [3,3]-sigmatropic rearrangement from **15**.



Furthermore, the concern that alkylation of the thioenolate **14** at carbon with allylic bromide **13d** in a S_N2' fashion would compete, appears to be unfounded. First attempts at [3,3]-sigmatropic rearrangement of the crude *S*-alkylthioenamine **15** under a variety of conditions (xylenes 140 °C, silylated glassware, high dilution, etc.) failed to produce the rearranged thiolactam **8** and yielded only complex mixtures of products. In the event that excess reagents from the *S*-alkylation of **14**, which were still present with the thioenamine **15**, were interfering with the rearrangement, it was decided to attempt the purification of the sensitive substrate **15**. Not unexpectedly, chromatography of the latter using a variety of adsorbent and solvent systems generally resulted in significant (∼35%) loss of material. The thioenamine **15**, obtained in pure form, was subjected to the [3,3]-sigmatropic rearrangement; however, the results were the same. This lack of rearrangement (**15** → **8**) proved especially disappointing in light of the fact that related systems had been shown earlier to undergo smooth thio-Claisen rearrangement (THF at 25 °C or xylenes at 140 °C).[7]

Finally, after extensive experimentation, it was discovered that *S-alkylthioenamine **15** underwent [3,3]-sigmatropic rearrangement in refluxing DME (83 °C for 96 h) to produce the desired bicyclic thiolactam **8***. The ^{1}H NMR spectrum derived from the crude product mixture indicated the presence of only two compounds in a 60:40 ratio, the thioenamine **15** and the desired rearranged product **8**, respectively. After chromatography, pure **8** was obtained in 34% yield. The relative and absolute stereochemistry depicted for **8** was assigned by analogy to the [3,3]-sigmatropic rearrangements of related substances

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from prior studies from this laboratory. In those earlier studies, the *S*-allylic moiety had rearranged to the exo(β) face of the bicyclic system via a chair conformation.[7] The failure to promote the thio-Claisen rearrangement in xylenes and its success in DME was initially unclear and therefore warranted further investigation. Furthermore, the [3,3]-sigmatropic rearrangement of the *S*-alkylthioenamine **15** into **8** in 34% yield certainly called for some improvement.

The use of ethereal solvent (DME) to perform the [3,3]-sigmatropic rearrangement allowed the transformation to become experimentally simple. Indeed, when the reaction mixture derived from the *S*-alkylation of **12** in DME was heated to reflux, the initially formed **15** underwent in situ thio-Claisen rearrangement into **8**. However, when **15** was heated in various ethereal solvents at reflux for longer periods of time (i.e., DME (85 °C) 13 days, dioxane (101 °C) 84 h, Bu_2O (140 °C) 48 h), the thiolactam **8** was obtained in 38, 37, and 32% isolated yields, respectively. The remainder of the thioenamine **15** remained unchanged. Furthermore, only a single diastereomer was formed during the [3,3]-sigmatropic rearrangement. It soon became obvious that prolonged heating or heating the thioenamine **15** at higher temperature did not increase the conversion to the key thiolactam **8**. The lack of complete conversion of **15** into **8** suggested that an equilibrium may be in operation wherein the rearrangement was reversible. Thus, thiolactam **8** was heated in refluxing Bu_2O (140 °C) for 3 h, and subsequent analysis of the ^{1}H NMR spectrum derived from the reaction mixture indicated the presence of both the thiolactam **8** and *S*-alkylthioenamine **15** in a 40:60 ratio, respectively, demonstrating conclusively the reversibility of the system. Although Claisen rearrangements are in principle reversible, the large driving force created by generating the more stable carbonyl group allows these reactions to be treated as irreversible.[8a] It has been reported that thio-Claisen rearrangements derived from a thioketone were found to be reversible.[16] However, the [3,3] rearrangements derived from the parent dithio esters and thioamides[17] are not known to be reversible and therefore, the equilibrium established between **15** and **8** appears to be unprecedented. In the O−Claisen rearrangement, it is known that *O*-alkylenol ethers derived from strained γ,δ-unsaturated carbonyl compounds have been observed to be reversible.[18]

Having established that the reversibility of the thio-Claisen process was responsible for the low (∼40%) conversion of the thioenamine **15** to the key thiolactam **8**, it now remained to study means to force the equilibrium ratio in favor of the product, **8**. Attempts to remove thiolactam **8** from the equilibrium via selective coordination of the thiocarbonyl moiety with a variety of Lewis acids (Pd(II) salts, Cu(I), MgBr, etc.) or via addition to the C−S double bond of **8** (KSCN, RMgBr, $(RO)_3P$, etc.) proved fruitless. A study to assess the effect of solvent polarity on the equilibrium position are summarized in Table 1. It is clear that the proportion of thiolactam **8** generally increased with solvent polarity (entries 1−7), whereas DMSO (entry 8) and the protic solvent systems (entries 9 and 10) led only to complex mixture of products. Interestingly, the rearrangement of **15** in HMPA or DMF solutions could only be conducted with purified material since the use of the crude *S*-alkylthioenamine **15** resulted in decomposition. However, this limitation was circumvented by adding K_2CO_3 (1.5 equiv) to the crude thioenamine−DMF solution, which appeared to neutralize any HBr that might have been released in the reaction mixture, as a result of decomposition of the small excess of allylic bromide **13d** used in the preceding *S*-alkylation. From the table it can be seen that nearly a 2:1 ratio of **8**:**15** was achieved in DMF at 90 °C after 72 h.

Table 1. Effect of Solvents and Temperature on the Equilibrium of **15**, **8**

entry	solvent	*T* (°C)	ratio **15:8**[a]
1	xylenes	140	100:0
2	MeCN	80	65:35
3	DME	83	60:40
4	dioxane	101	60:40
5	Bu_2O	140	60:40
6	HMPA	100	48:52
7	DMF	90	36:64
8	DMSO	80	dec[b]
9	H_2O:MeOH (3:1)	90	dec
10	EtOH	78	dec

[a] Ratio determined via integration of the benzylic protons of **15** and **8** in the ^{1}H NMR spectrum of the crude reaction mixture. [b] dec = decomposition.

In light of the limited, yet beneficial, influence of solvent on the equilibrium mixture, it was possible to conduct the rearrangement in DMF which produced the desired thiolactam **8** in 50% isolated yield as well as 22% of **15**. After separation, resubjecting the latter substance under identical conditions provided an additional 10% of the thiolactam **8**. In this fashion, a 60% overall yield of **8** was achieved.

Having access to reasonable yields of the thiolactam **8**, the chiral auxiliary now had to be removed. However, the thiolactam proved to be resistant to reduction conditions previously employed for related bicyclic lactam systems (Red-Al, low temperature).[19] By employing Meerwein's reagent in refluxing CH_2Cl_2, the thiolactam **8** formed the corresponding thioiminium ion[7] **16**, which was efficiently reduced with Red-Al (−78 °C) in situ to the thioaminal **17**. The latter material was subjected to hydrolysis in $EtOH/H_2O/Bu_4NH_2PO_4$ to liberate the chiral keto-aldehyde **7**, which underwent spontaneous aldol condensation to the desired 4,4-disubstituted enone **6** in a reasonable 54% overall yield from **8**. This material exhibited spectroscopic data identical with that of Pearson's racemic material,[6d] except for chiroptical properties: $[\alpha]^{25}_D$ −131° (c = 1.37/$CHCl_3$). The enone **6** was subsequently treated with methylene triphenylphosphorane in benzene at room temperature to afford the corresponding triene **18** in 92% yield. Finally, dissolved metal reduction (Na/NH_3) of triene **18** at −78 °C afforded (−)-trichodiene (**1**) along with the 1,2-reduction product **19** as an 85:15 mixture, respectively. Chromatography of the mixture over $AgNO_3$ impregnated silica afforded the volatile (−)-trichodiene (**1**) in 65% isolated yield. This material exhibited a rotation of −18 ($CHCl_3$), which compares somewhat favorably with the reported rotation for the natural trichodiene of +21.[1] However, further confirmation of the enantiomeric purity was sought. A sample of enantiomerically enriched (−)-trichodiene was obtained from Professor Jack Gilbert; chiral GLC analysis

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(18) For some recent examples of retro-Claisen rearrangements, see: (a) Boeckman, R. K., Jr.; Reeder, M. R. *J. Org. Chem.* **1997**, *62*, 6456−6457. (b) Boeckman, R. K., Jr.; Shair, M. D.; Vargas, J. R.; Stolz, L. A. *J. Org. Chem.* **1993**, *58*, 1295−1297. (c) Boeckman, R. K., Jr.; Flann, C. J.; Poss, K. M. *J. Am. Chem. Soc.* **1985**, *107*, 4359−4362. For a theoretical treatment of pericyclic reactions see: (d) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984−6986. (e) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983−6984. (f) Carpenter, B. K. *Tetrahedron* **1978**, *54*, 1877−1884.

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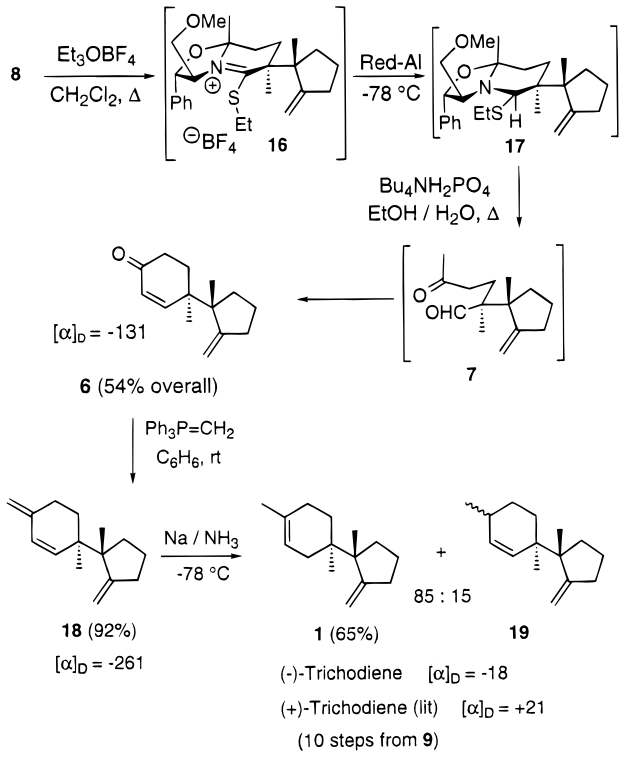

of his sample showed the ratio of enantiomers to be 67:33. When the synthetic sample obtained in this study was injected onto the chiral column (Experimental Section), only the peak corresponding to (−)-trichodiene was visible, indicating the enantiomeric purity of **1** ($[\alpha]_D = -18$) was indeed greater than 99%. The specific rotation, therefore, was subject to the usual experimental errors that normally plague polarimetric determinations. Furthermore, all other physical data (IR, NMR, *m*/*e*) were in complete agreement with those reported for the natural material.[1a]

In conclusion, we have achieved the asymmetric synthesis of (−)-trichodiene in 10 steps and 14% overall yield from the readily available bicyclic lactam **9**. The thio-Claisen rearrangement has proven to be a powerful synthetic tool in the preparation of a key synthetic intermediate bearing vicinal stereogenic quaternary centers. The [3,3]-sigmatropic transposition, derived from *S*-alkylthioenamine **15**, was shown to be reversible, and the equilibrium ratio of the rearranging partners was shown to be somewhat solvent dependent. Further work on the development of new synthetic methods to access chiral, nonracemic, quaternary carbon substances via the thio-Claisen rearrangement are in progresss.

Experimental Section

Thin-layer chromatography (TLC) and flash chromatography were performed with E. Merck silica gel (230−400 mesh). TLC grade flash chromatography was performed using Sigma Type H silica gel (10−40 μm, no binder). All reagents were purchased from Aldrich. All nonaqueous reactions were conducted under an argon atmosphere in oven or flame-dried apparatus. All solvents and reagents were purified using established procedures. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Bicyclic Lactam 11. To a cold (−78 °C) stirred solution of LDA (42.2 mmol) in dry THF (150 mL) was added bicyclic lactam **10**[11] (10.57 g, 38.4 mmol) in THF (40 mL) via a cannula. The reaction mixture was allowed to stir for 15 min, then MeI (5.50 g, 2.51 mL, 38.8 mmol) was added. The solution was stirred for 15 min at −78 °C, warmed to room temperature, stirred for an additional 1 h, and treated with saturated aqueous NH_4Cl (50 mL). The mixture was diluted with Et_2O (500 mL) and the layers were separated. The organic layer was washed with H_2O (2 × 75 mL) and brine (50 mL), dried over $MgSO_4$, and then filtered; the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (4:1 to 1.5:1 Hex−EtOAc gradient) to afford 9.69 g (87%) of an epimeric mixture (1.2:1) of the bicyclic lactam **11** as a colorless solid. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, 3H, J = 7.2 Hz), 1.57 (s, 3H), 1.60−1.70 (m, 1H), 1.72−1.85 (m, 1H), 2.00−2.14 (m, 1H), 2.20 (dt, 1H, J = 12.2, 2.7 Hz), 2.35−2.44 (m, 1H), 3.34 (s, 3H), 3.62 (dd, 1H, J = 3.1, 10.2 Hz), 3.76 (dd, 1H, J = 5.4, 10.2 Hz), 4.02−4.10 (m, 1H), 5.23 (d, 1H, J = 6.8 Hz), 7.25−7.43 (m, 5H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 24.1, 26.4, 35.4, 36.8, 59.2, 63.3, 70.8, 78.5, 93.6, 126.6, 128.2, 128.5, 139.3, 172.6. IR (KBr pellet): 2930, 1641, 1403 cm^{-1}. HRMS (FAB+) for $C_{17}H_{24}NO_3$ $(M + H)^+$: calcd 290.1756, found 290.1751.

Bicyclic Thiolactam 12. To a stirred solution of bicyclic lactam **11** (9.00 g, 31.1 mmol) in dry toluene (80 mL), was added Belleau's reagent[12] (9.04 g, 17.1 mmol). The reaction mixture was heated to reflux for 1 h, then cooled to room temperature, and the solvent was removed under reduced pressure. The residue was filtered through Florisil (CH_2Cl_2 as eluent) and the solvent was removed under reduced pressure. The residue was purified via flash chromatography (13:1 to 6:1 Hex−EtOAc gradient) to afford 8.24 g (87%) of an epimeric mixture (2:1) of the bicyclic thiolactam **12** as a colorless solid. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, 3H, J = 6.6 Hz), 1.55−1.60 (m, 1H), 1.61 (s, 3H), 1.79−1.92 (m, 1H), 2.09−2.21 (m, 1H), 2.25 (dt, 1H, J = 11.9, 3.3 Hz), 2.86−3.00 (m, 1H), 3.36 (s, 3H), 3.71 (dd, 1H, J = 2.8, 10.6 Hz), 4.20 (dd, 1H, J = 4.7, 10.6 Hz), 4.54−4.61 (m, 1H), 5.39 (d, 1H, J = 7.9 Hz), 7.26−7.45 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 25.3, 26.1, 34.8, 44.5, 59.3, 68.2, 68.6, 77.7, 95.2, 126.7, 128.5, 128.6, 138.6, 203.4. IR (KBr pellet) 2923, 1441 cm^{-1}. HRMS (FAB+) for $C_{17}H_{24}NO_2S$ $(M + H)^+$: calcd 306.1528, found 306.1527. Anal. Calcd for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59; N, 4.59. Found: C, 67.01; H, 7.50; N, 4.49.

(2-Methylcyclopent-1-yl)methanol (13c). To a cold (−78 °C) stirred slurry of $LiAlH_4$ (2.55 g, 67.2 mmol) in dry Et_2O (150 mL) was added carboxylic acid **13b**[13] (5.64 g, 44.8 mmol) portionwise over 20 min. The reaction mixture was warmed slowly to room temperature and allowed to stir overnight. The mixture was cooled to 0 °C and saturated aqueous NH_4Cl (50 mL) was added cautiously. The precipitate was filtered and rinsed with Et_2O (2 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, and filtered; the solvent was removed under reduced pressure. The residue was distilled (85−86 °C/13 mmHg) to afford 3.74 g (75%) of the alcohol **13c**[14] as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 1H), 1.67 (s, 3H), 1.79 (quint, 2H, J = 7.5 Hz), 2.26−2.35 (m, 2H), 2.38−2.37 (m, 2H), 4.16 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 21.4, 34.0, 38.6, 58.8, 134.1, 135.5. IR (thin film): 3320, 2841 cm^{-1}.

1-(Bromomethyl)-2-methylcyclopentene (13d). To a cold (0 °C) stirred suspension of NBS (0.76 g, 4.3 mmol) in dry CH_2Cl_2 (20 mL) was added Me_2S (0.29 g, 0.34 mL, 4.7 mmol). The resulting yellow suspension was stirred at 0 °C for 15 min; then the alcohol **13c** (410 mg, 3.66 mmol) was added in CH_2Cl_2 (3 mL) via a cannula. The reaction mixture was allowed to slowly warm to room temperature over 3.5 h. The mixture was diluted with hexanes (50 mL), washed with H_2O (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and then was filtered. The solvent was removed under reduced pressure and the residue was distilled (bulb-to-bulb, 35−40 °C/1 mmHg) from CaH_2 and Cu wire into a receiving bulb cooled to −78 °C containing Cu wire. Obtained was 445 mg (70%) of the unstable allylic bromide **13d**[15] as a light yellow oil, which was stored immediately at −20 °C for a period not exceeding 2−3 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 3H), 1.82 (quint, 2H, J = 7.4 Hz), 2.32 (m, 2H), 2.45 (m, 2H), 4.07 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.1, 29.9, 34.5, 38.9, 131.3, 139.7. IR (thin film) 2953, 1664, 1446, 1198 cm^{-1}.

Bicyclic Thioenamine 15. To a cold (0 °C) stirred solution of LDA (2.49 mmol) in dry THF (20 mL) was added the bicyclic thiolactam **12** (637 mg, 2.09 mmol) in THF (2.5 mL) via a cannula. The reaction mixture was allowed to stir for 20 min, and 1-(bromomethyl)-2-methylcyclopentene (**13d**, 436 mg, 2.49 mmol) was added in THF (2.5

mL) via a cannula. The mixture was stirred at 0 °C for 5 min, then warmed to room temperature and was allowed to stir for an additional 20 min. The solution was diluted with Et_2O (50 mL), washed with 1 M NaOH (2 × 10 mL), H_2O (10 mL) and brine (10 mL), dried over K_2CO_3, and filtered; the solvent was removed under reduced pressure. The thick yellow oil obtained was generally subjected to the [3,3]-sigmatropic rearrangement without further purification owing to its instability to chromatography. A sample from a related experiment was purified via flash chromatography (33:1 Hex−EtOAc containing 0.3% Et_3N) to provide the thioenamine **15** as a thick yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.60 (s, 3H), 1.67−1.93 (m, 8H; therein 1.89 (s, 3H)), 2.18−2.53 (m, 5H), 3.12 (d, 1H, J = 12.8 Hz), 3.35 (s, 3H), 3.51 (d, 1H, J = 12.8 Hz), 3.67 (ddd, 1H, J = 3.9, 5.7, 8.2 Hz), 3.77 (dd, 1H, J = 8.2, 9.2 Hz), 3.89 (dd, 1H, J = 3.9, 9.2 Hz), 5.10 (d, 1H, J = 5.7 Hz), 7.18−7.32 (m, 3H), 7.36−7.42 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 21.4, 21.5, 26.0, 27.2, 31.7, 34.2, 35.6, 38.5, 58.9, 69.5, 75.5, 79.8, 94.4, 120.8, 126.4, 127.2, 128.1, 131.8, 133.6, 134.9, 142.0. IR (thin film) 2924, 1448, 1099 cm^{-1}.

Bicyclic Thiolactam 8. The crude thioenamine **15** (2.09 mmol) prepared above was dissolved in dry DMF (21 mL), anhydrous K_2CO_3 (433 mg, 3.13 mmol) was added, and the reaction mixture was heated to 90 °C for 72 h. The reaction mixture was cooled to room temperature and poured into brine (200 mL). The aqueous layer was extracted with Et_2O (5 × 20 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (10 mL), dried over K_2CO_3 and filtered; the solvent was removed under reduced pressure. The residue, which was shown (^{1}H NMR) to be a mixture (36:64) of **15** and **8**, respectively, was subjected to flash chromatography (TLC grade silica gel,[20] 13:1 Hex−EtOAc) to afford 183 mg (22%) of thioenamine **15** as well as 414 mg (50%) of the bicyclic thiolactam **8** as a thick light yellow oil, which solidified upon storage at −20 °C. The recovered thioenamine was resubjected to thermal rearrangement under identical experimental conditions as described above to provide an additional 85 mg (10%) of the bicyclic thiolactam **8**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38−1.88 (m, 15H; therein 1.57 (s, 3H), 1.62 (s, 3H), 1.68 (s, 3H)), 1.91−2.00 (m, 1H), 2.07−2.15 (m, 1H), 2.21−2.45 (m, 2H), 3.33 (s, 3H), 3.68 (dd, 1H, J = 2.8, 10.5 Hz), 4.00 (dd, 1H, J = 4.7, 10.5 Hz), 4.88 (ddd, 1H, J = 2.8, 4.7, 8.2 Hz), 4.93 (d, 1H, J = 2.8 Hz), 4.95 (d, 1H, J = 1.9 Hz), 5.36 (d, 1H, J = 8.2 Hz), 7.25−7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 22.8, 25.3, 26.3, 29.8, 33.0, 37.9, 38.7, 51.4, 53.3, 59.0, 68.4, 68.7, 77.5, 95.6, 106.8, 126.7, 128.3, 128.5, 138.8, 159.2, 206.5. IR (thin film) 2958, 1394 cm^{-1}. HRMS (FAB+) for $C_{24}H_{34}NO_2S$ $(M + H)^+$: calcd 400.2310, found 400.2315. Anal. Calcd for $C_{24}H_{33}NO_2S$: C, 72.14; H, 8.32; N, 3.51. Found: C, 72.00; H, 8.26; N, 3.44. $[\alpha]^{25}_D$ −281° (c = 1.11/$CHCl_3$).

(4*R*)-4-Methyl-4-((1*S*)-1-methyl-2-methylcyclopent-1-yl)-cyclohex-2-enone (6). To a stirred solution of bicyclic thiolactam **8** (129 mg, 0.322 mmol) in dry CH_2Cl_2 (5 mL) was added Et_3OBF_4 (2 M in CH_2Cl_2, 0.39 mL, 0.77 mmol), and the mixture was heated to reflux for 2 h. The resulting red solution was cooled to −78 °C and a solution of Red-Al (65% in toluene, 0.126 mL, 0.406 mmol) was added dropwise. The mixture was allowed to stir for 20 min, then was treated with 1 M NaOH (1 mL) and warmed to room temperature. The mixture was diluted with Et_2O (15 mL), washed with 1 M NaOH (2 × 2 mL), H_2O (2 mL) and brine (2 mL), dried over K_2CO_3, and then filtered; the solvent was removed under reduced pressure. The residue acquired was taken up in EtOH (3 mL)/H_2O (3 mL)/$Bu_4NH_2PO_4$ (1 M in H_2O, 6 mL), and the solution was heated to reflux for 15 h. The mixture was cooled to room temperature and the EtOH was removed under reduced pressure. The aqueous layer was poured into brine (25 mL) and was extracted with Et_2O (5 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried over K_2CO_3, and filtered; the solvent was removed under reduced pressure. The oil thus obtained was subjected to flash chromatography (19:1 Hex−EtOAc) to afford 35.8 mg (54%) of the enone **6** as a clear colorless oil.[6d] A pure sample for HRMS and optical rotation was obtained by distillation (190−200 °C/0.6 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.19 (s, 3H), 1.39−1.55 (m, 2H), 1.64−1.90 (m, 3H), 2.11 (dt, 1H, J = 5.0, 13.8 Hz), 2.19−2.31 (m, 1H), 2.32−2.43 (m, 2H), 2.53 (ddd, 1H, J = 5.5, 14.2, 17.2 Hz), 4.86 (d, 1H, J = 2.7 Hz), 5.04 (d, 1H, J = 2.7 Hz), 5.91 (dd, 1H, J = 1.0, 10.4 Hz), 6.98 (dd, 1H, J = 2.1, 10.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 23.2, 24.5, 29.4, 34.1, 37.2, 38.3, 41.5, 49.4, 107.5, 127.8, 156.9, 158.3, 199.5. IR (thin film) 2958, 2871, 1682, 1612 cm^{-1}. HRMS (FAB+) for $C_{14}H_{21}O$ $(M + H)^+$: calcd 205.1592, found 205.1586. $[\alpha]^{25}_D$ −131° (c = 1.37/$CHCl_3$).

(1*R*)-1-Methyl-1-((1*S*)-1-methyl-2-methylcyclopent-1-yl)-4-methylenecyclohex-2-ene (18). To a stirred mixture of Ph_3PCH_2, prepared from Ph_3PCH_3Br (0.18 g, 0.51 mmol) and a solution of *n*-BuLi (2.10 M in hexanes, 0.19 mL, 0.41 mmol), in dry benzene (10 mL) was added the enone **6** (41.7 mg, 0.204 mmol) in benzene (2 mL) via a cannula. The mixture was allowed to stir at room temperature for 2.5 h and then diluted with hexanes (45 mL). The organic layer was washed with H_2O (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, and then filtered; the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (Hex) and the resulting oil was distilled (bulb-to-bulb, 140−150 °C/0.8 mmHg) to afford 38 mg (92%) of the triene **18** as a clear colorless oil.[6d] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.07 (s, 3H), 1.32−1.56 (m, 3H), 1.58−1.88 (m, 3H), 2.17−2.52 (m, 4H), 4.73 (s, 1H), 4.76 (s, 1H), 4.83 (d, 1H, J = 3.0 Hz), 4.98 (d, 1H, J = 2.0 Hz), 5.85 (d, 1H, J = 10.0 Hz), 6.07 (d, 1H, J = 10.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 23.3, 24.5, 27.1, 30.2, 37.3, 38.5, 40.6, 49.5, 106.6, 109.8, 127.9, 137.0, 143.0, 159.5. IR (thin film) 2954, 1642 cm^{-1}. $[\alpha]^{25}_D$ −261° (c = 1.59/$CHCl_3$).

(−)-Trichodiene (1). To a cold (−78 °C) stirred solution of sodium (12 mg, 0.52 mmol) in ammonia (predried from Na) was added a solution of the triene **18** (25 mg, 0.12 mmol) in dry THF (2 mL) via a cannula. The reaction mixture was stirred for 1 h, then treated with *t*-BuOH (0.5 mL) and allowed to stir for an additional 5 min. The flask was removed from the cooling bath and the ammonia was allowed to evaporate. The residue was dissolved in hexanes (20 mL) and the organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, and then filtered; the solvent was removed under reduced pressure to afford a mixture (85:15) of (−)-trichodiene (**1**) and the 1,2-reduction product **19**, respectively. This mixture was subjected to flash chromatography (hexanes as eluent) over $AgNO_3$ impregnated silica (12.5% in CH_3CN) and (−)-trichodiene (**1**) was isolated as the fast running band. The derived oil was distilled (bulb-to-bulb, 180 °C/1 mmHg) to afford 16.3 mg (65%) of (−)-trichodiene (**1**) as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.04 (s, 3H), 1.32−1.51 (m, 3H), 1.56−2.08 (m, 10H; therein 1.64 (s, 3H)), 2.13−2.28 (m, 1H), 2.32 (dd, 1H, J = 6.6, 14.0 Hz), 4.74 (d, 1H, J = 2.7 Hz), 4.96 (d, 1H, J = 2.7 Hz), 5.27−5.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 23.3, 23.4, 24.0, 27.8, 28.1, 33.0, 36.8, 37.2, 38.9, 50.6, 106.8, 120.5, 132.3, 159.9. IR (thin film) 3065, 2958, 890 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{24}$ $(M)^+$: calcd 204.1878, found 204.1872. $[\alpha]^{25}_D$ −18° (c = 0.50/$CHCl_3$), lit.[1a] (+)-trichodiene $[\alpha]_D$ +21°. Chiral GLC analysis (Chiraldex B−PH) proved the sample of (−)-trichodiene to be >99% enantiomerically pure when compared to a sample of enantiomerically enriched (−)-trichodiene[6a] exhibiting the following retention times: (−)-trichodiene, 10.58 min (67%); (+)-trichodiene, 15.43 min (33%). The sample from the present study appeared at 10.58 min with no visible trace of the (+)-enantiomer. Further mixing of the two samples gave only the peaks at 10.58 (enhanced) and 15.43 min.

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Supporting Information Available: Spectral data (^{1}H and ^{13}C) of all key intermediates and chiral GLC traces of the final products (15 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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