Studies on enolate chemistry of 8-thiabicyclo[3.2.1]-octan-3-one: enantioselective deprotonation and synthesis of sulfur analogs of tropane alkaloids

Marek Majewski, Marc DeCaire, Pawel Nowak, and Fan Wang

Abstract: Enantioselective deprotonation of 8-thiabicyclo[3.2.1]octan-3-one (**1**) with chiral lithium amides, followed by reactions with electrophiles affords sulfur analogs of tropane alkaloids of pyranotropane family. Thus, deprotonation of **1** with (*S*)-*N*-(diphenyl)methyl-1-phenylethylamine (**11d**), followed by the reaction of the resulting nonracemic enolate with benzaldehyde gives the corresponding aldol product as one diastereoisomer (*exo*, threo) and in high enanatiomeric purity (95% ee). Trimethylsilyl chloride, acetic anhydride, and acyl cyanides react readily with the lithium enolate to give the corresponding derivatives of **1**, however common alkylating agents fail to provide *C*-alkylated products. The reaction with acyl cyanides derived from α,β-unsaturated carboxylic acids (e.g., cinnamoyl cyanide) can be utilized in synthesis of thia-analogs of tropane alkaloids physoperuvine and isobellendine (**13**, **15**).

Key words: enantioselective deprotonation, tropane alkaloids.

Résumé : La déprotonation énantiosélective de la 8-thiabicyclo[3.2.1]octan-3-one à l'aide d'amides de lithium chiraux, suivie de réactions avec des électrophiles, conduit à la formation d'analogues sulfurés des alcaloïdes du tropane, de la famille du pyranotropane. Ainsi, la déprotonation du produit **1** avec de la (*S*)-*N*-(diphényl)méthyl-1-phényléthylamine (**11d**), suivie d'une réaction de l'énolate non racémique qui en résulte avec du benzaldéhyde, conduit à la formation du produit aldolique correspondant, sous la forme d'un diastéréoisomère (*exo*, thréo) et avec une pureté énantiotopique éleveée (95% ee). Le chlorure de triméthylsilyle, l'anhydride acétique et les cyanures d'acyles réagissent facilement avec l'énolate de lithium pour conduire à la formation des dérivés correspondants du produit **1**. Toutefois, les agents alkylants habituels ne conduisent pas à la formation de produits *C*-alkylés. On peut toutefois utiliser la réaction avec des cyanures d'acyles dérivés d'acides carboxyliques α,β-insaturés (par exemple, le cyanure de cinnamoyle) pour effectuer la synthèse de la physopéruvine et de l'isobellendine, des analogues sulfurés des alcaloïdes du tropane (**13**, **15**).

Mots clés : déprotonation énantiosélective, alcaloïdes du tropane.

[Traduit par la Rédaction]

Introduction

8-Thiabicyclo[3.2.1]octan-3-one (**1**) is a simple, readily available symmetrical ketone that can be viewed as a potential scaffold for construction of diverse compounds of medium complexity and, perhaps most notably, as a scaffold for construction of sulfur analogs of tropane alkaloids. These alkaloids comprise a group of over 200 natural products of general structure **2** (R groups are typically alkyls or acyls, brackets signify that the group can be at e.g., C-2 or C-4, R and R′ can be connected forming a heterocycle), built around a common 8-azabicyclo[3.2.1]octane skeleton (1). During the last few years we have developed a comprehensive strategy for stereoselective synthesis of tropane alkaloids based on enantioselective deprotonation of tropinone (**3**) with chiral lithium amides (e.g., **4**) as the key reaction. A number of tropane alkaloids were synthesized (2–5), and an elegant synthesis of cocaine utilizing our strategy, which allowed setting up the absolute and relative stereochemistry around all 4 stereogenic centers in 2 steps, has recently been reported by Cha and co-workers (6). Replacement of the nitrogen atom in a biologically active natural product by the sulfur atom is a well known strategy in medicinal chemistry often leading to substantial changes in biological activity of the compound (7, 8). TBON had been used as a replacement for alkaloid intermediates during studies on alkaloid metabolism and on biosynthesis of cocaine (9). We were interested in developing a general synthesis of sulfur analogs of tropane alkaloids and, towards this end, we initiated an investigation of lithiation of **1** with chiral lithium amides and of reactions of the corresponding enolate.

Enantioselective deprotonation of symmetrical ketones (note the enantiotopic protons in structures **1** and **3**) with chiral lithium amides is a relatively new methodology (2,

Received April 20, 2001. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on November 19, 2001.

Dedicated to Professor Victor Snieckus, lithiator extraordinarie.

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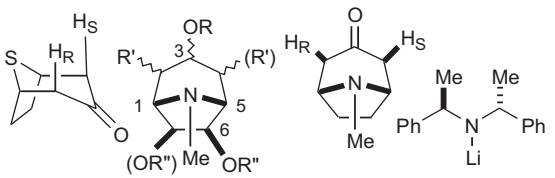
 DOI: 10.1139/cjc-79-11-1792



1 2 3 4

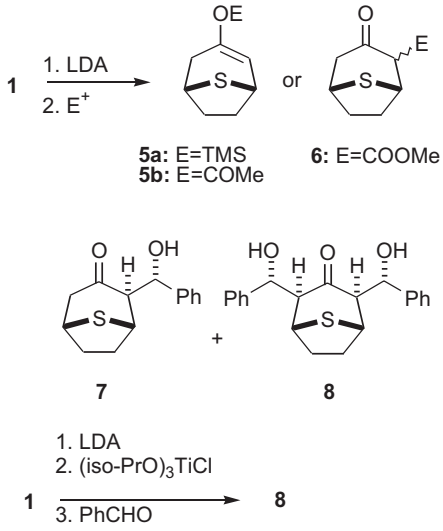
10). A number of diverse ketones have been investigated over the last decade and, even though the mechanism of the reaction is still not fully understood, several trends have emerged: (*i*) certain level of conformational rigidity is necessary for achieving high level of enantioselectivity. Thus, 4-*tert*-butylcyclohexanone could be deprotonated with higher enantioselectivity than the 4-methyl analog (11). (*ii*) Bicyclic, bridged ketones are especially good substrates in reaction with chiral lithium amides (high enantioselectivity) (2, 10). (*iii*) Addition of certain salts, especially LiCl, can be very beneficial from the standpoint of reaction selectivity (12). (*iv*) There is no straightforward correlation between the structure of the ketone, the lithium amide, and selectivity. There is no magic bullet; certain lithium amides can be very selective with some ketones but show poor selectivity in other systems. Thus, every new system must be researched experimentally. It should be noted that a few other heterocyclic compounds containing sulfur have been investigated in the context of enantioselective deprotonation (13, 14). One precedent involving TBON was reported previously by Simpkins and co-workers (15), who also noted a strong effect of the $ZnCl_2$ additive on the selectivity of deprotonation with the chiral base **4**.

On the basis of the foregoing TBON looked like a promising substrate for synthesis using deprotonation with chiral lithium amides as the key step, but it should be emphasized that, as with any new system, the conditions for successful selective deprotonation had to be elaborated from the beginning. Apart from being interesting in the purely theoretical sense TBON could provide a useful starting material for construction of α-substituted cycloheptanones (after desulfurization), and it should be noted that the presence of the sulfur atom in the bridge offers potential for much more diverse chemistry than the corresponding carbon-, oxygen-, or nitrogen-bridged systems due to the ability of dialkylsulfur compounds to exist in three oxidation states (as sulfides, sulfoxides, or sulfones).

Results and discussion

Since little was known about chemical properties of TBON we started by running a series of typical experiments. Lithiation of **1** with LDA proceeded in the usual fashion and the resulting enolate could be efficiently trapped with TMS-Cl, Ac_2O, benzaldehyde, or methyl cyanoformate to afford the corresponding silyl enol ether **5a** (96% isolated yield), enol acetate **5b** (97%), aldol product **7** (92%), or β-ketoester **6** (98%), respectively (Scheme 1). We were, however, unable to effect alkylation of TBON lithium enolate. Most of the attempts with reactive alkylating agents: methyl or ethyl iodide, benzyl bromide, or butyl tosylate gave numerous products that were difficult to purify; in some cases the starting material was recovered. It should be noted that similar failures of the well-known, and all too often taken for granted, alkylation reaction were observed before in cases involving other ketone enolates (16).

Scheme 1.

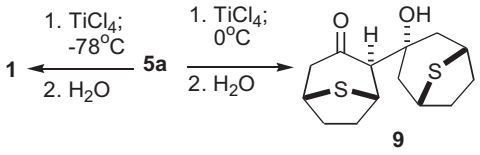


The aldol reaction leading to product **7** proceeded with very high diastereoselectivity and only one isomer out of possible four diastereoisomeric aldols was formed (to the limit of the NMR detection in the crude product). In analogy to tropinone (2) we have assigned the *exo–anti* relative configuration (as drawn) to this compound. The *exo* orientation of the CHOHPh group was also supported by NOE studies. The proton NMR spectrum of the crude aldol product indicated a presence of a minor by-product (ca. 6% by integration). We made no effort to isolate this product from the mixture, but we believe it to be the bis-aldol **8**. Compound **8** was produced in good yield (61%) in a separate experiment involving the titanium enolate of **1** (Scheme 1) and the NMR spectrum of **8** was consistent with the *exo*,*exo*,*anti*,*anti* relative configuration. In the mixture, the bis-aldol **8** could be easily confused with the expected minor product i.e., the *syn* isomer of the aldol **7**, because the benzylic protons of this compounds appear ca. 0.35 ppm downfield of the signal characteristic of the benzylic proton of compound **7**; an accidental juxtaposition of signals resembling a typical mixture of erythro (*syn*) and threo (*anti*) aldols (17). The formation of a bis-aldol as the major product of addition of the titanium enolate of TBON to benzaldehyde is unusual — the expected result would be the *syn* isomer of **7** as the major product (18).

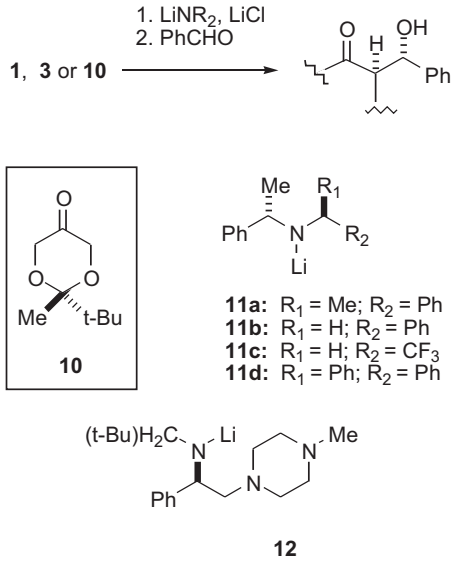
Some oxygen-bridged ketones similar to **1** are known to undergo a ring opening to the corresponding cycloheptenone derivatives upon treatment of their silyl enol ethers with Lewis acids (19). In an attempt to recreate this reaction on TBON, we treated the TMS enolate **5a** with titanium tetrachloride (Scheme 2). There was no evidence of ring opening, however, depending on the reaction temperature, either the self-aldol product **9** was formed in good yield (70% of **9** was isolated when the experiment was done at 0°C) or, at low temperature, the enol ether was presumably cleanly transmetalated and, upon quenching, converted cleanly and quantitatively into the parent ketone **1**.

Having achieved reasonable predictability of behavior of the TBON enolate a brief experimental study of enantio-

Scheme 2.

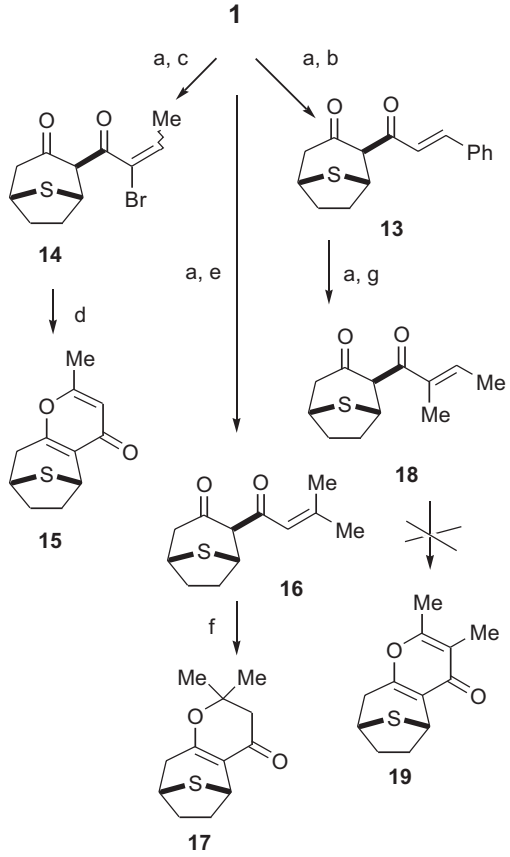


Scheme 3.



selective deprotonation was launched. The chiral lithium amides used in this study are shown in Scheme 3; the aldol addition to benzaldehyde was used as the model reaction because the enantiomeric excess (ee) could be easily measured on the aldol **7** using NMR with a chiral solvating agent [(*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol]. The absolute stereochemistry of deprotonation has not been established, but, by analogy to tropinone, we believe that the major, dextrorotatory enantiomer of **7**, which was produced in each case, should be as drawn in Scheme 1. The results are summarized in Table 1, which also includes, for comparison, enantioselectivities attained using the same reagents with other heterocyclic ketones: tropinone **3** and dioxanone **10**. All reactions were done in the presence of LiCl (one mol per one mol of the amide). The reaction with base **4** (i.e., with the enantiomer of **11a**) had been previously reported to proceed with 84% ee (15). Despite numerous attempts the highest ee in our experiments was 70% (as measured by NMR on the crude product; the optical purity of the sample could be easily increased by crystallization). The reaction seemed to be fairly capricious and substantial amounts of the bis-aldol were observed in all experiments involving base **11a** (15–25%). We also noticed that in experiments that yielded more bis-aldol product the optical purity of compound **7** was higher (e.g., 58% ee of **7** at **7**:**8** ratio of 85:15 and 70% ee of **7** at **7**:**8** ratio of 75:25), suggesting that the second aldol reaction had introduced an element of kinetic resolution. In an effort to optimize this reaction we tried a number of conditions and finally we observed that the best selectivity was consistently achieved when the amine hydrochloride was

Scheme 4. Reagents: (*a*) LiCl; (*b*) PhCH=CHCOCN; (*c*) MeCH=CBrCOCN; (*d*) Et_3N; (*e*) Me_2C=CHCOCN; (*f*) Na_2CO_3, EtOH; (*g*) MeCH=CMeCOCN.



used to generate the LiCl–$LiNR_2$ mixture in situ (19) and when the ketone was added slowly (over 90 min) to the solution of the amide (see *Experimental*). All experiments were subsequently run under these conditions. The most selective base turned out to be compound **11d** (Table 1, entry 4). It was interesting to note that bases **11a** and **12**, which provided high selectivity in tropinone deprotonation, were ineffective in both the TBON and the dioxanone systems, and conversely, base **11d** by far the best as far as TBON deprotonation was concerned, performed worse than other bases with substrate **3**, and gave only modest selectivity with compound **10**. Amide **11c**, developed by Aoki and Koga (20) and known to be selective in several systems (2, 21) was not very effective with TBON.

We had previously described stereoselective syntheses of a number of tropane alkaloids via the enantioselective deprotonation strategy (2). Extension of this approach to synthesis of sulfur analogs of tropane alkaloids e.g., chalcostrobamine and darlingine appeared straightforward. Enantioselective deprotonation of TBON with the chiral amide **11d** followed by treatment of the resulting enolate with an acyl cyanide (Scheme 4) proceeded readily to give the corresponding β-diketone (**13**, **14**, **16**, or **18**). The sulfur analog of chalcostrobamine **13** was produced in a modest yield of 61%, even though an analogous reaction with LDA (leading to the racemate of **13**) was very efficient (92% yield). Acylation with 2-bromo-2-butenoyl cyanide gave compound

Table 1. Results of enantioselective deprotonation of TBON (**1**), followed by reaction with benzaldehyde.

		TBON (**1**)			Tropinone	Dioxanone
Entry	Base	ee (%)	**7**:**8**	Yield (%)[a]	**3** ee (%)[b]	**10** ee (%)[c]
1	**11a**	70	75:25	80	90	59
2	**11b**	45	90:10	78	—	39
3	**11c**	70	95:5	72	88	90
4	**11d**	95	98:2	82	87	70
5	**12**	74	90:10	75	94	20

Note: Literature data for analogous reactions on tropinone and dioxanone are provided for comparison.
[a]Combined yield of **7** and **8**.
[b]Refs. 2–4.
[c]Refs. 2, 12, and 21.

14 that, without purification, was converted into a sulfur analog of isobellendine **15** by heating with triethylamine. This sequence of three reactions was quite efficient (48% overall yield, 87% ee). Compound **17**, which is not an analog of a known tropane alkaloid, was produced by a similar reaction sequence (78% yield, 92% ee). We have also attempted a synthesis of a sulfur analog of darlingine, but, even though the acylation proceeded well, we were unable to find an efficient method to introduce the double bond into the pyranone ring. Overall, enantioselective deprotonation of TBON coupled with acylation using acyl cyanides provided an easy entry into sulfur analogs of alkaloids of pyranotropane family.

Experimental

All air sensitive reactions were carried out under nitrogen. Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium and benzophenone. Dichloromethane and diisopropylamine were distilled from calcium hydride. Lithium chloride was dried at 130–150°C in vacuum overnight and it was used as a solid or as a solution in tetrahydrofuran. *n*-Butyllithium was periodically titrated using 2,5-dimethoxybenzyl alcohol. Flash column chromatography (FCC) and dry flash chromatography (DFC) were carried out using Merck silica gel 60 (230–400 mesh) and Sigma silica gel Type H (10–40 μm), respectively. Thin layer chromatography (TLC) was performed on precoated glass plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm) or with a developing solution by charring on a hot plate. The developing solution was prepared by dissolving concentrated sulfuric acid (50 g), cerium(IV) sulfate (10 g), and phosphomolybdic acid hydrate (40 g) in water (1 L). Optical rotations were measured on a Elmer 241 Polarimeter (1 dm, 1 mL cell), all concentrations are given in g per 100 mL. Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer in chloroform-*d* solvent unless otherwise noted. Chemical shifts are reported in ppm of δ scale with TMS as the internal standard. Coupling constants (*J*) are reported to the nearest 0.5 Hz.

General procedure A

Diisopropylamine (0.17 mL, 1.20 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0°C. *n*-BuLi (0.44 mL, 2.5 M solution in hexanes, 1.10 mmol) was added dropwise and the solution was stirred for 0.5 h at 0°C was cooled to –78°C, and then **1** (0.142 g, 1.00 mmol) in THF (0.5 mL) was added dropwise over 1 min. The resulting mixture was then stirred for 2 h. Next, the electrophile (1.20 mmol) was added. After 0.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was then allowed to warm up to room temperature. Water was added (20 mL) and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (1 × 20 mL), brine (1 × 20 mL), and dried ($MgSO_4$). The solvent was then removed (rotovap) and the product was purified by dry flash chromatography (hexane → hexane–ethyl acetate, 1:1).

General procedure B

Hydrochloride of the chiral amine **11** (1.10 mmol) was dissolved in THF (10 mL) and cooled to 0°C. *n*-BuLi (0.88 mL, 2.5 M solution in hexanes, 2.20 mmol) was added dropwise and the solution was stirred for 1.5 h. After cooling the amide solution to –78°C, compound **1** (0.142 g, 1.00 mmol) in THF (1.0 mL) was added dropwise over 0.5 h (syringe pump). The resulting mixture was then stirred for 2 h and the electrophile (1–1.2 mmol) in THF (1 mL) was added. After 0.5 h the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and was then allowed to warm up to room temperature. Water was added (20 mL) and the mixture was extracted with diethyl ether or with chloroform (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (1 × 20 mL), brine (1 × 20 mL), and dried ($MgSO_4$). The solvent was then removed. The amount of side product (e.g., **8**) and the ee of the main product (e.g., **7**) was next determined by ^{1}H NMR In experiments involving the aldol **7** samples were prepared by dissolving the product (2.5 mg) and the chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE, 10.0 mg) in C_6D_6 (0.5 mL). The signal at 5.07 ppm showed best splitting and was used to determine ee. The crude product was then purified by dry flash chromatography (hexane → hexane–ethyl acetate, 1:1).

8-Thiabicyclo[3.2.1]octan-3-one (1)

This compound was prepared according to the literature procedure (9*a*). Yield 50%. R_f = 0.3 (hexane–ethyl acetate,

4:1). ^{1}H NMR δ: 3.84–3.79 (m, 2H), 2.78 (dd, *J* = 20.0, 3.0 Hz, 2H), 2.65 (dd, *J* = 16.5, 3.0 Hz, 2H), 2.24–2.07 (m, 2H), 2.07–1.95 (m, 2H). ^{13}C NMR δ: 208.8, 52.8, 45.4, 34.2.

8-Thiabicyclo[3.2.1]oct-2-en-3-yl trimethylsilane (5a)

Diisopropylamine (1.19 mL, 8.40 mmol) was dissolved in THF (50 mL) and cooled to 0°C. *n*-BuLi (3.08 mL, 2.5 M solution in hexanes, 7.70 mmol) was added dropwise and the solution stirred for 0.5 h. After cooling the amide solution to –78°C, trimethylchlorosilane (2.14 mL, 16.80 mmol) was added followed by 8-thiabicyclo[3.2.1]octan-3-one (0.994 g, 7.00 mmol) in THF (5 mL). The resulting mixture was then stirred for 1 h at –78°C and then for 1 h at 0°C. The reaction mixture was then allowed to warm up to room temperature. The solvents and the excess of trimethylsilane were removed and the residue was dissolved in diethyl ether (100 mL). The solution was next washed with saturated aqueous $NaHCO_3$ solution (3 × 25 mL), brine (1 × 25 mL), and dried ($MgSO_4$). The solvent was then removed in vacuum and the product purified by dry flash chromatography (hexane → hexane–ethyl acetate, 4:1). The product was obtained as colorless semisolid (1.435 g, 96%). R_f = 0.59 (hexane–ethyl acetate, 4:1). ^{1}H NMR δ: 5.33 (d, *J* = 7.5 Hz, 1H), 3.89–3.80 (m, 1H), 3.69–3.60 (m, 1H), 2.68–2.56 (m, 1H), 2.38–2.12 (m, 2H), 2.10–1.82 (m, 3H), 0.13 (s, 9H). ^{13}C NMR δ: 150.0, 111.5, 45.6, 43.5, 43.3, 41.6, 34.4, 0.2.

8-Thiabicyclo[3.2.1]oct-2-en-3-ol acetate (5b)

Lithium enolate of 8-thiabicyclo[3.2.1]octan-3-one was generated according to the general procedure A. Acetic anhydride (0.13 mL, 1.25 mmol) was added to the enolate solution. The reaction mixture was stirred at –78°C for 1 h and then at 0°C for another 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was then allowed to warm up to room temperature. Water was added (20 mL) and the mixture extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (1 × 20 mL), brine (1 × 20 mL), and dried ($MgSO_4$). The solvent was then removed in vacuum and the product purified by dry flash chromatography (hexane → ethyl acetate). The product (0.177 g, 97%) was obtained as colorless semisolid. R_f = 0.37 (hexane–ethyl acetate, 4:1). EI-MS *m*/*z* (%): 184 (M^+, 40), 149 (28), 142 (100), 114 (25), 113 (53), 109 (27), 99 (18). HRMS calcd. for $C_9H_{12}O_2S$: 184.0558; found: 184.0559. IR (cm^{-1}): 1755, 1208, 1115. ^{1}H NMR δ: 5.90 (d, *J* = 7.5 Hz, 1H), 3.98–3.90 (m, 1H), 3.78–3.70 (m, 1H), 2.80–2.70 (m, 1H), 2.52–2.41 (m, 1H), 2.33–2.19 (m, 2H), 2.18–2.00 (m, 2H), 2.09 (s, 3H). ^{13}C NMR δ: 169.0, 147.8, 120.9, 45.2, 42.8, 40.9, 40.0, 34.2, 20.8.

2-Methoxycarbonyl-8-thiabicyclo[3.2.1]octan-3-one (6)

This compound was synthesized via lithium enolate of **1** as described in general procedure A. Methyl cyanoformate (0.10 mL, 1.25 mmol) was used as the electrophile. The product (0.180 g, 98%) was obtained as a clear oil, which was comprised of 3 isomers in a ratio of 52:15:33 (established by ^{1}H NMR integration of the OCH_3 signal). Since these compounds could not be separated due to easy equilibration, characterization was done on the acetate derivative. Compound **6** (0.180 g, 0.98 mmol) was dissolved in pyridine (5 mL) and acetic anhydride was added (1 mL). The reaction mixture was stirred at rt for 24 h. Next, water was added (20 mL) and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL), brine (1 × 20 mL), and dried ($MgSO_4$). The solvent was then removed and the product was purified by dry flash chromatography (hexane → hexane–ethyl acetate, 1:1), which yielded a colorless oil (0.221 g, 98%). R_f = 0.23 (hexane–ethyl acetate, 1:1). EI-MS *m*/*z* (%): 242 (M^+, 9), 200 (64), 169 (18), 168 (100), 140 (22), 139 (10). HRMS calcd. for $C_{11}H_{14}O_4S$: 242.0613; found: 242.0607. IR (cm^{-1}): 1765, 1715, 1202, 1163. ^{1}H NMR δ: 4.38 (d, *J* = 5.0 Hz, 1H), 3.89–3.77 (m, 1H), 3.72 (s, 3H), 2.90–2.62 (m, 1H), 2.51–2.40 (m, 1H), 2.30 (dd, *J* = 18.5, 2.5 Hz, 1H), 2.24–2.10 (m, 2H), 2.17 (s, 3H), 2.08–1.97 (m, 1H). ^{13}C NMR δ: 168.4, 164.0, 155.9, 125.7, 51.8, 45.0, 44.0, 42.3, 40.8, 34.6, 20.8.

***exo*-2-(Hydroxybenzyl)-8-thiabicyclo[3.2.1]octan-3-one (7)**

Compound **7** was obtained as described in general procedure A and was further purified by using one of the following methods:

Method 1: The crude aldol product (containing some residual amine and bisaldol **8**) was taken in hexane (40 mL) and brought to reflux. The heating was removed and dichloromethane was added dropwise till the aldol product became soluble. The solution was left in an open flask for 3 h, after which time long needle crystals of **7** (76%) were collected.

Method 2: The crude aldol product was purified by dry flash chromatography (hexane → hexane–ethyl acetate, 1:1) which yielded pure **7** (90%) and **8** (6% when LDA was used as the base): mp 140–142°C. R_f = 0.38 (hexane–ethyl acetate, 1:1). EI-MS *m*/*z* (%): 248 (M^+, 24), 142 (100), 114 (21), 113 (44), 109 (18), 107 (34), 106 (21), 105 (34), 85 (20), 70 (43), 77 (60). HRMS calcd. for $C_{14}H_{16}O_2S$: 248.0871; found: 248.0868. IR (cm^{-1}): 3438, 1706, 1051. ^{1}H NMR ($CDCl_3$) δ: 7.47–7.28 (m, 5H), 5.13 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.40 (s, 1H), 3.16–3.12 (m, 1H), 3.05–2.96 (m, 1H), 2.81 (d, *J* = 2.5 Hz, 1H), 2.75–2.71 (m, 1H), 2.71–2.66 (m, 1H), 2.10–1.82 (m, 4H). ^{1}H NMR (C_6D_6) δ: 7.39–7.30 (m, 2H), 7.28–7.03 (m, 3H), 5.07 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.03–2.90 (m, 2H), 2.84 (d, *J* = 3.0 Hz, 1H), 2.58–2.47 (m, 2H), 2.23 (dd, *J* = 16.5, 3.0 Hz, 1H), 1.57–1.22 (m, 4H). ^{13}C NMR δ: 210.8, 141.0, 128.7, 128.3, 127.0, 75.3, 66.6, 51.6, 48.4, 45.8, 33.8 (2 signals). Note: optically active compound was synthesized using procedure B with chiral Li-amide **11d**. After one recrystallization the compound was enantiomerically pure: $[\alpha]_D^{25}$ +105.7 (*c* 2.04, CH_2Cl_2; c.f., ref. 15).

Compound 8

The lithium enolate of **1** (1.00 mmol) was generated as described in procedure A. Triisopropoxytitanium chloride (0.690 g, 3.00 mmol) was added and the mixture was kept at –78°C for 1 h, warmed up to 0°C and cooled again to –78°C. Benzaldehyde (3.00 mmol, 0.31 mL) was added and the mixture was stirred for another 4 h. The reaction was quenched with water (20 mL), extracted with diethyl ether (3 × 50 mL), dried with anhydrous $MgSO_4$, and

the solvent was evaporated. The ratio of **7**:**8** (18:82) was measured by ^{1}H NMR. The crude mixture was purified by dry flash chromatography (dichloromethane → dichloromethane–ethyl acetate, 1:1), which yielded pure **8** as a white solid (0.217 g, 61%) and pure **7** (0.038 g, 13%).

Properties of **8**: mp 162–164°C. R_f = 0.59 (hexane–ethyl acetate, 1:1). CI-MS (NH_3) *m*/*z* (%): 304 (27), 232 (17), 231 (87), 162 (63), 160 (19), 143 (16), 142 (80), 124 (20), 114 (50), 109 (15), 106 (24), 105 (100), 94 (29), 91 (14), 81 (15), 78 (23), 77 (24), 74 (19), 61 (65). IR (cm^{-1}): 3510, 1701, 1190, 1050. ^{1}H NMR δ: 7.50–7.28 (m, 10H), 5.45 (d, *J* = 9.5 Hz, 2H), 3.20–3.10 (m, 2H), 2.85 (d, *J* = 8.0 Hz, 2H), 2.07–1.80 (m, 6H). ^{13}C NMR δ: 210.5, 141.2, 128.8, 128.5, 127.0, 75.9, 68.0, 48.9, 33.4.

Compound 9

8-Thiabicyclo[3.2.1]oct-2-en-3-yl trimethylsilane (**5a)** (0.320 g, 1.50 mmol) was dissolved in dichloromethane (10 mL), the solution was cooled down to –78°C, and $TiCl_4$ (0.17 mL, 1.50 mmol) was added. The mixture was stirred for 1 h at –78°C and then for 2 h at 0°C. The reaction was then quenched with saturated solution of $NaHCO_3$ (10 mL). Diethyl ether (100 mL) was added, and the organic phase was separated and washed with saturated $NaHCO_3$ (2 × 25 mL), brine (25 mL), and dried with $MgSO_4$. The solvent was evaporated under vacuum and the product was subjected to dry flash chromatography (hexane → hexane–ethyl acetate, 4:1), which yielded two products: **1** (0.037 g, 17%) and **9** (0.150 g, 70%).

Properties of **9**: mp 135–137°C. R_f = 0.19 (hexane–ethyl acetate, 4:1). EI-MS *m*/*z* (%): 284 (M^+, 8), 266 (60), 233 (28), 142 (100), 114 (35), 99 (24), 85 (68), 69 (82). HRMS calcd. for $C_{14}H_{20}O_2S_2$: 284.0905; found: 284.0909. IR (cm^{-1}): 3435, 1696, 1052. ^{1}H NMR δ: 4.18–4.05 (br s, 1H), 3.96–3.87 (m, 1H), 3.83–3.75 (m, 1H), 3.71–3.63 (m, 1H), 3.61–3.52 (m, 1H), 2.88–2.77 (m, 1H), 2.66–1.77 (m, 14H). ^{13}C NMR δ: 208.7, 72.9, 68.7, 53.3, 46.8, 46.5, 46.3, 45.9, 45.8, 45.5, 33.8, 33.4, 33.0, 32.9.

(–)-2-Cinnamoyl-8-thiabicyclo[3.2.1]octan-3-one (13)

Lithium enolate of **1** (0.5 mmol) was prepared as described in procedure B (base **11d**). After stirring at –78°C for 3 h, cinnamoyl cyanide (100 mg, 0.60 mmol) in THF (1 mL) was added to the enolate, and the resulting mixture was stirred at –78°C for 30 min, followed by quenching with 40% K_2CO_3 (2 mL). After warming up to rt, the reaction mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and the solvent was removed under vacuum. Column chromatography (SiO_2, hexane–ethyl acetate, 4:1) afforded the pure product **13** as a yellow oil (83 mg, 61%). This product had 87% ee as determined by NMR with (*S*)-(+)-TFAE. $[\alpha]_D^{25}$ –330 (*c* 0.99, MeOH). R_f = 0.40 (hexane–ethyl acetate, 4:1). HRMS calcd. for $C_{16}H_{16}O_2S$: 272.0871; found: 272.0866. IR (cm^{-1}): 1626, 1576, 1558, 1540. ^{1}H NMR δ: 7.67 (d, *J* = 15.5 Hz, 1H), 7.60–7.54 (m, 2H), 7.43–7.33 (m, 3H), 7.01 (d, *J* = 15.5 Hz, 1H), 4.56–4.49 (m, 1H), 3.92–3.78 (m, 1H), 3.00 (dd, *J* = 19.0, 6.0 Hz, 1H), 2.58 (dd, *J* = 19.0, 2.0 Hz, 1H), 2.40–2.20 (m, 4H), 2.10–1.93 (m, 1H). ^{13}C NMR δ: 199.3, 169.8, 140.9, 135.3, 129.9, 128.8, 127.9, 117.6, 116.5, 48.8, 44.4, 44.0, 40.0, 34.5.

5,5-Dimethyl-6-oxa-12-thia-tricyclo[7.2.1.0^{2,7}]dodec-2(7)-en-3-one (17)

Lithium enolate of **1** (0.5 mmol) was prepared according to procedure B (base **11d**). Senecioyl cyanide (0.055 mL, 0.72 mmol) in THF (1 mL) was added, and the resulting mixture was stirred at –78°C for 30 min, followed by quenching with 40% K_2CO_3 (2 mL). After warming up to rt the reaction mixture was extracted with ether (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and the solvent was removed under vacuum to give the crude product **16**. Compound **16** was subjected to cyclization without purification: the entire sample was dissolved in EtOH (7 mL), anhydrous Na_2CO_3 (0.14 g) was added, and the mixture was heat at reflux for 1 h. The solvent was then removed under vacuum, the residue was taken in ether and the carbonate was filtered off. Column chromatography (hexane–EtOAc, 4:1) afforded the product **17** as a white solid (91 mg, 81%). This sample had 92% ee as determined by HPLC using a ChiraDex 250–4 column (Merck), an UV detector (at 254 nm) in 50% MeOH – phosphate buffer (pH = 6.8, *c* = 0.025 M), flow: 0.4 mL min^{-1}. mp 90–92°C (note: racemate mp 75–77°C). $[\alpha]_D^{25}$ –94.1 (*c* 1.03, MeOH). R_f = 0.20 (hexane–EtOAc, 4:1). EI-MS *m*/*z* (%): 224 (100), 209 (76), 168 (26), 155 (13), 140 (44), 135 (11), 97 (12), 85 (10), 83 (10), 79 (17), 71 (23). IR (cm^{-1}): 1652, 1603. ^{1}H NMR δ: 1.35 (s, 3H), 1.37 (s, 3H), 1.80–1.88 (m, 1H), 2.10–2.31 (m, 4H), 2.42 (d, *J* = 16.6 Hz, 1H), 2.49 (d, *J* = 16.6 Hz, 1H), 2.79 (dq, *J* = 18.6, 2.1 Hz, 1H), 3.87(m, 1H), 4.55 (m,1H). ^{13}C NMR δ: 25.8, 27.2, 34.4, 40.1, 40.6, 42.3, 45.0, 47.3, 80.5, 119.5, 168.4, 188.3. Anal. calcd. for $C_{12}H_{16}O_2S$: C 64.26, H 7.19; found: C 64.47, H 7.17.

5-Methyl-6-oxa -12-thia-tricyclo[7.2.1.0^{2,7}]dodeca-2(7)-4-dien-3-one (15)

Lithium enolate of **1** (0.5 mmol) was generated according to procedure B (base **11d**). 2-Bromo-2-butenoyl cyanide (95 mg, 97%, 0.53 mmol) in THF (1 mL) was then added and the resulting mixture was stirred at –78°C for 30 min. followed by quenching with 40% K_2CO_3 (2 mL). After warming up to rt the reaction mixture was extracted with ether (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and the solvent was removed under vacuum to give the crude product **14** that was refluxed over 3 h in triethylamine (5 mL). The solvent (Et_3N) was then removed under vacuum. The residues were basified with 40% K_2CO_3 (10 mL) and extracted with ether (3 × 10 mL). The extracts were dried over $MgSO_4$. After removal of the solvent, column chromatography afforded the product as oil (53 mg, 51%). This sample had 87% ee as determined by ^{1}H NMR with (*S*)-(+)-TFAE. R_f = 0.50 (CH_2Cl_2–MeOH, 9:1). EI-MS *m*/*z* (%): 208 (100), 180 (65), 179 (34), 175 (55), 161 (13), 91 (9),77 (5). HRMS calcd. for $C_{11}H_{12}O_2S$: 208.0557 (M^+); found: 208.0558. IR (cm^{-1}): 1659, 1611, 1596. ^{1}H NMR δ: 1.82–1.93 (m, 1H), 2.16 (s, 3H), 2.10–2.40 (m, 3H), 2.52 (dd, *J* = 18.1, 2.3 Hz, 1H), 3.08 (dq, *J* = 18.1, 2.1 Hz, 1H), 3.95 (m, 1H), 4.67 (d, *J* = 4.9 Hz, 1H), 6.03 (s, 1H). ^{13}C NMR δ: 20.0, 34.6, 39.8, 40.4, 40.5, 44.9, 113.5, 129.6, 162.3, 165.1, 176.1. Note:

racemic **15** produced via an analogous synthesis using LDA (mp 89–91°C).

Acknowledgments

The authors thank Natural Sciences and Engineering Research Council of Canada (NSERC) and the University of Saskatchewan for financial support of this project (for a preliminary communication, see ref. 22).

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