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Sterically Constrained 'Roofed' 2-Thiazolidinones as Excellent Chiral Auxiliaries

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The "roofed" chiral 2-thiazolidinones, which are sterically congested and conformational rigid, and which are prepared by the [4+2] cycloaddition of 2-thiazolone to the cyclic dienes, dimethylanthracene and hexamethylcyclopentadiene, followed by optical resolution with (1S,2R)-2-methoxy-1-apocamphanecarbonic acid (MAC acid) are of considerable promise for use as chiral auxiliaries for the alkylation of enolates.

Key words 2-thiazolone; [4+2] cycloadduct; 2-thiazolidinone; chiral auxiliary; optical resolution

Methods involving the use of heterocyclic chiral auxiliaries for a wide range of asymmetric transformations have been highly successful, in terms of the stereoselective construction of a number of natural products and biologically important compounds. Of the heterocyclic auxiliaries which have been explored thus far, the chiral 2-oxazolidinones[1)] and 2-imidazolidinones[2)] hold considerable promise, because of their high versatility and high degrees of asymmetric induction.

We previously reported on the preparation of sterically congested and conformationally fixed 2-oxazolidinones and 2-imidazolidinones with "roofed" structures such as **1** (**a**: DMAOx[3)], **b**: DMAIm[4)]) and **2** (**a**: HMCOx[5)], **b**: HMCIm[6)]). These substances serve as excellent chiral auxiliaries in enantiocontrolled typical transformations ranging from alkylations to Michael type additions as well as Diels–Alder reactions.

This paper describes the facile synthesis of the "roofed" type of chiral 2-thiazolidinones **8**—**11** with the same steric demands as those of the tricyclic compounds **1** and **2**, in which conformational rigidity and steric shielding, largely the result of the bridgehead methyl groups, would allow these compounds to serve as highly promising chiral auxiliaries, as previously pointed out.[3—6)]

By simply heating the 3-acetyl-2-thiazolone[7)] **3**, which is readily derived from commercially available 2-bromothiazole, with a slight excess of 9,10-dimethylanthracene **4** and 1,1,2,3,4,5-hexamethylcyclopentadiene[8)] **5** at 140 °C, the uncatalyzed cycloaddition reaction proceeded smoothly to give the [4+2] cycloadducts, **6a** and **7a**, respectively. The straightforward optical resolution of the resulting cycloadducts was performed in a manner analogous to that used in the preparation of the same types of 2-oxazolidinones (**1a**, **2a**)[3,5)] and 2-imidazolidinones (**1b**, **2b**).[4,6)] The cycloadducts **6c** and **7c**, after deacetylation with cesium carbonate in methanol, were converted with the aid of (1*S*,2*R*)-2-methoxy-1-apocamphanecarbonyl chloride (MAC chloride)[9)] to the readily separable *N*-acylated diastereomers **8b**, **9b** and **10b**, **11b**, respectively, in which the MAC auxiliary was smoothly removed with the $LiBH_4$–MeOH agents,[10)] to give nearly quantitative yields of both enantiomers. These simple and high yield processes are of practical use for a relatively large scale preparation of the cycloadduct-based chiral, crystalline 2-thiazolidinones **8c**—**11c**.

The stereochemistry of the sterically constrained 2-thiazo-

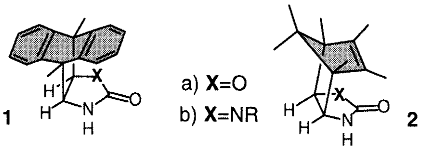

Fig. 1

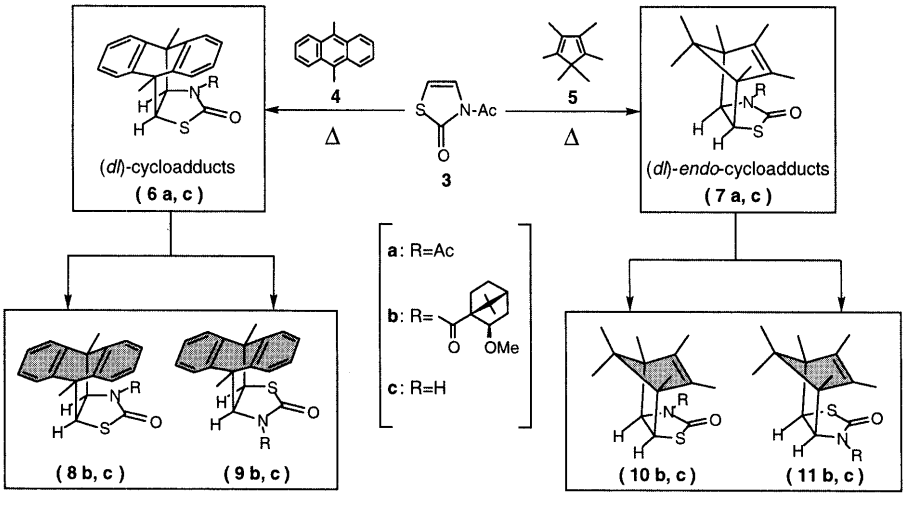

Chart 1

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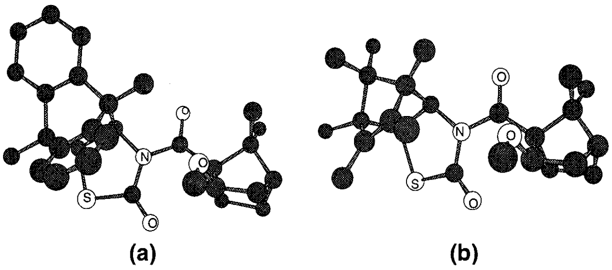
Dedicated to the memory of Dr. Kyosuke Tsuda.

lidinone chiral auxiliaries **8c** and **10c** thus obtained was unequivocally confirmed by X-ray crystal analysis[11] of the *N*-MAC isomers **8b** and **10b**, as shown in Fig. 2.



(a) **(b)**

Fig. 2. Perspective View of **8b** (**a**) and **10b** (**b**) by X-Ray Analysis

The high potential of this type 2-thiazolidinones as chiral auxiliaries was demonstrated by diastereocontrolled alkylations of the *N*-acyl-2-thiazolidinones (**12**—**15**) *via* the enolates. As can be seen in Table 1, the reactions proceeded with high to excellent diastereoselectivity, as expected, and both types of compounds **8c** (**9c**) and **10c** (**11c**) were equally effective for a high level of asymmetric induction, although the latter gave a somewhat higher selectivity on treatment with Lithium bis(trimethyl silyl) amide (LHMDS) as a base.[12] Even in the case of the methylation of *N*-butyryl-2-thiazolidinone enolates with methyl iodide, a reaction which is generally difficult to control with high degrees of diastereoselection,[10a,13] an excellent diastereomer ratio of 118 : 1 was obtained using auxiliary **10c**.

In conclusion, newly synthesized 2-thiazolidinones **8c**—**11c**, which are conformationally fixed and sterically congested, all serve equally well as useful chiral heterocyclic auxiliaries, which belong to the same category of excellent chiral 2-oxazolidinone and 2-imidazolidinone auxiliaries (**1**, **2**) which have been previously developed.[3—6]

Experimental

General Methods Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP 370 polarimeter. ^{1}H-NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard on a JEOL ALPHA-500 (500 MHz) and JEOL JNM-GX400 (400 MHz) spectrometers. MS and HRMS were obtained with a JEOL JMS-DX303HF mass spectrometer. Column chromatography was performed using Silica gel 60 (70—230 mesh, Merck). HPLC analysis was performed on a COSMOSIL® column (Nacalai Tesque, Inc.). Capillary gas chromatography was performed on a Shimadzu GC-14A equipped with a flame ionization detector using a TC-17 column. X-ray crystallographic data was measured on a Rigaku AFC7R diffractometer with graphite monochromated Cu*K*α radiation and a rotating anode generator. All solvents were distilled prior to use; THF over Na/benzophenone, Et_2O over $LiAlH_4$, CH_2Cl_2 over CaH_2, MeOH over NaOMe and benzene over CaH_2.

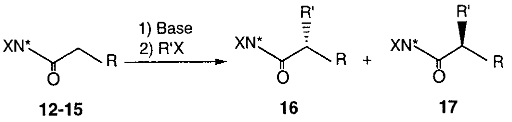
3-Acetyl-2-thiazolone (3) The reaction mixture of 2-bromothiazole (5.0 g) and NaOH (3.6 g) in *tert*-butyl alcohol (30 ml) was refluxed with stirring for 2 d, after which time and acetic anhydride (30 ml) was added. The reaction mixture was then heated at 100 °C for an additional 2 h. Removal of the precipitates followed by evaporation *in vacuo* and chromatographic purification on silica gel (hexane–AcOEt (20 : 1)) gave 3-acetyl-2-thiazolone (**3**) (2.2 g, 51%) as colorless crystals, mp 37—38 °C (from CH_2Cl_2–hexane). ^{1}H-NMR δ: 2.62 (3H, s), 6.25 (1H, d, J=6.1 Hz), 7.36 (1H, d, J=6.1 Hz). *Anal.* Calcd for $C_5H_5NO_2S$: C, 41.95; H, 3.52; N, 9.78. Found: C, 41.71; H, 3.37; N, 9.55.

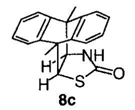
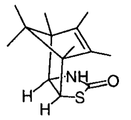
(*dl*)-5-Acetyl-1,7-dimethyl-3-thio-5-aza-dibenzo[h,k]tricyclo[5.2.2.0^{2,6}]-undeca-8,10-dien-4-one (6a) The solution of 3-acetyl-2-thiazolone (**3**) (1.0 g, 7.0 mmol) and 9,10-dimethylanthracene (**4**) (1.6 g, 7.7 mmol) in *m*-xylene (7.0 ml) was heated at 150—160 °C in a sealed tube for 8 d. Removal of the solvent, followed by chromatography on silica gel (CH_2Cl_2) gave the *N*-acetyl-cycloadducts **6a** (2.2 g, 89%) as colorless crystals, mp 238—239 °C (from CH_2Cl_2–hexane). ^{1}H-NMR δ: 1.86 (3H, s), 1.95 (3H, s), 2.43 (3H, s), 3.89 (1H, d, J=9.7 Hz), 4.97 (1H, d, J=9.7 Hz), 7.22—7.40 (8H, m). *Anal.* Calcd for $C_{21}H_{19}NO_2S$: C, 72.18; H, 5.48; N, 4.01. Found: C, 72.18; H, 5.24; N, 3.99.

(*dl*)-1,7-Dimethyl-3-thio-5-aza-dibenzo[h,k]tricyclo[5.2.2.0^{2,6}]undeca-8,10-dien-4-one (6c) A solution of the *N*-acetyl-cycloadducts **6a** (2.1 g, 6.0 mmol) in MeOH (6.0 ml) was treated with Cs_2CO_3 (0.2 g, 0.6 mmol) at room temperature for 2 h. The mixture was acidified with 3 M aqueous solution of citric acid and extracted with AcOEt. The usual work-up followed by chromatographic purification on silica gel (CH_2Cl_2–AcOEt (9 : 1)) gave the crystalline *N*-deacetylated cycloadducts **6c** (1.5 g, 81%), mp >300 °C (from EtOH). ^{1}H-NMR δ: 1.92 (3H, s), 1.93 (3H, s), 3.89 (1H, d, J=9.7 Hz), 4.03 (1H, d, J=9.7 Hz), 6.08 (1H, br), 7.20—7.34 (8H, m). *Anal.* Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56. Found: C, 74.23; H, 5.36; N, 4.35.

5-[(1*S*,2*R*)-2-Methoxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carbonyl]-1,7-dimethyl-3-thio-5-aza-dibenzo[h,k]tricyclo[5.2.2.0^{2,6}]undeca-8,10-dien-4-ones. Diastereoisomers, 8b and 9b To a solution of *N*-deacetylated cycloadducts **6c** (2.3 g, 7.3 mmol) and BuLi (1.5 M hexane solution; 5.4 ml, 8.0 mmol) in THF (70 ml), the MAC chloride prepared from (1*S*,2*R*)-7,7-dimethyl-2-methoxybicyclo[2.2.1]heptane-1-carboxylic acid (MAC acid) (1.6 g, 8.0 mmol) was added along with an excess $SOCl_2$ and the entire reaction mixture was heated at 50 °C for 5 h. The mixture was treated with a saturated aqueous solution of NH_4Cl and extracted with AcOEt. The usual work-up gave a diastereomeric mixture of the *N*-MAC derivatives which were cleanly separated by chromatography on silica gel (CH_2Cl_2–hexane

Table 1. Diastereoselective Alkylation of Chiral *N*-Propionyl and *N*-Butyryl-2-thiazolidinones (**12**—**15**)



HXN*	R	Base (1.05 eq)	R′X	Temp (°C)	Yield (%)[a]	**16** : **17**
 **8c**	Me (**12**)	NaHMDS	$PhCH_2Br$	−78	68	53 : 1[b]
	Me (**12**)	NaHMDS	$CH_2=CHCH_2Br$	−78	56	39 : 1[b]
	Et (**13**)	NaHMDS	CH_3I	−78	93	32 : 1[b]
 **10c**	Me (**14**)	LHMDS	$PhCH_2Br$	−30	87	110 : 1[c]
	Me (**14**)	LHMDS	$CH_2=CHCH_2Br$	−30	71	>300 : 1[c]
	Et (**15**)	LHMDS	CH_3I	−30	90	66 : 1[c]
	Et (**15**)	LHMDS	CH_3I	−50	91	118 : 1[c]

a) Isolated yields. *b*) Determined by HPLC analysis. *c*) Determined by capillary GC.

(3 : 7)) to give the *N*-MAC diastereomers **8b** (1.6 g, 44%) and **9b** (1.6 g, 44%).

Isomer **8b**: mp 215—216 °C (from CH_2Cl_2–hexane). $[\alpha]_{\mathrm{D}}^{27}$ −235.4° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 1.04—1.08 (1H, m), 1.14 (3H, s), 1.34 (3H, s), 1.61—1.71 (4H, m), 1.86—1.98 (2H, m), 1.92 (3H, s), 1.93 (3H, s), 3.17 (3H, s), 3.95 (1H, d, J=10.3 Hz), 4.25—4.28 (1H, m), 5.19 (1H, d, J=10.3 Hz), 7.18—7.40 (8H, m). *Anal.* Calcd for $C_{30}H_{33}NO_3S$: C, 73.89; H, 6.82; N, 2.87. Found: C, 73.76; H, 6.94; N, 2.71.

X-Ray Crystal Data for **8b**: $C_{30}H_{33}NO_3S$, monoclinic, $P2_1$, a=13.246(2) Å, b=8.326(2) Å, c=11.720(1) Å, β=98.478(9)°, V=1278.4(4) Å^3, Z=2, μ(Cu$K\alpha$)=13.37 cm^{-1}, R=0.060.

Isomer **9b**: mp 182—183 °C (from CH_2Cl_2–hexane). $[\alpha]_{\mathrm{D}}^{29}$ +232.4° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 1.09—1.10 (1H, m), 1.17 (3H, s), 1.32 (3H, s), 1.57—1.63 (2H, m), 1.78—1.80 (2H, m), 1.84 (3H, s), 1.89—1.91 (1H, m), 1.93 (3H, s), 2.05—2.09 (1H, m), 3.07 (3H, s), 3.92 (1H, d, J=9.7 Hz), 4.13—4.15 (1H, m), 5.17 (1H, d, J=9.7 Hz), 7.20—7.37 (8H, m). *Anal.* Calcd for $C_{30}H_{33}NO_3S$: C, 73.89; H, 6.82; N, 2.87. Found: C, 73.97; H, 6.86; N, 2.92.

(−)-1,7-Dimethyl-3-thio-5-aza-dibenzo[h,k]tricyclo[5.2.2.0^{2,6}]undeca-5H-8,10-dien-4-one [(−)-DMATh] (8c) A solution of diastereomer **8b** (0.4 g, 0.8 mmol) in THF (8.3 ml) was treated with $LiBH_4$ (3.4 mmol)–MeOH (0.3 ml) at 50 °C for 10 h. Purification of the deacylated product by chromatography on silica gel (hexane–AcOEt (9 : 1)) gave the (−)-enantiomer **8c** as colorless crystals (0.25 g, 99%), mp 125—126 °C (from EtOH). $[\alpha]_{\mathrm{D}}^{27}$ −122.5° (c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56. Found: C, 74.39; H, 5.70; N, 4.55.

(+)-1,7-Dimethyl-3-thio-5-aza-dibenzo[h,k]tricyclo[5.2.2.0^{2,6}]undeca-5H-8,10-dien-4-one [(+)-DMATh] (9c) A similar treatment of the *N*-MAC isomer **9b** (0.6 g, 1.2 mmol) as above gave the (+)-enantiomer **9c** (0.22 g, 58%) as colorless crystals, mp 121—122 °C (from EtOH). $[\alpha]_{\mathrm{D}}^{25}$ +123.6° (c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56. Found: C, 74.36; H, 5.69; N, 4.52.

(*dl*)-5-Acetyl-1,7,8,9,10,10-Hexamethyl-3-thio-5-azatricyclo[5.2.1.0^{2,6}]-dec-8-en-4-one (7a) A solution of 3-acetyl-2-thiazolone (**3**) (2.0 g, 13.9 mmol) and hexamethylcyclopentadiene[8] (**5**) (3.14 g, 20.9 mmol) in *m*-xylene (7.0 ml) was heated at 150—160 °C in a sealed tube for 3 d. Removal of the solvent, followed by chromatography on silica gel (hexane–AcOEt (9 : 1)) gave the cycloadducts **7a** (2.0 g, 49%) as a yellow oil. ^{1}H-NMR δ: 0.67 (3H, s), 0.79 (3H, s), 1.01 (3H, s), 1.10 (3H, s), 1.50 (3H, d, J=1.2 Hz), 1.67 (3H, d, J=1.2 Hz), 2.42 (3H, s), 3.80 (1H, d, J=9.1 Hz), 4.96 (1H, d, J=9.1 Hz). MS (FAB) *m*/*z*: 294 (MH^+), 252, 150.

(*dl*)-1,7,8,9,10,10-Hexamethyl-3-thio-5-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-one (7c) Analogous to the procedure for **6c**, deacetylation of cycloadducts **7a** (1.3 g, 4.4 mmol) with Cs_2CO_3 (0.1 g, 0.4 mmol) gave crystalline **7c** (0.9 g, 86%), mp 185 °C (from hexane). ^{1}H-NMR δ: 0.68 (3H, s), 0.70 (3H, s), 0.99 (3H, s), 1.04 (3H, s), 1.58 (3H, d, J=1.2 Hz), 1.68 (3H, d, J=1.2 Hz), 3.97 (1H, d, J=9.1 Hz), 4.02 (1H, d, J=9.1 Hz), 6.50 (1H, br). *Anal.* Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57. Found: C, 66.68; H,8.43; N, 5.53.

5-[(1*S*,2*R*)-7,7-Dimethyl-2-methoxybicyclo[2.2.1]heptane-1-carbonyl]-1,7,8,9,10,10-hexa-methyl-3-thio-5-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-ones. Diastereoisomers 10b and 11b By analogy with the cycloadducts **6c**, **7c** (0.5 g, 1.9 mmol) was acylated with the MAC chloride to give the diastereomeric *N*-MAC derivatives which were cleanly separated by chromatography on silica gel (CH_2Cl_2–hexane (3 : 7)) to the diastereomers **10b** (0.4 g, 47%) and **11b** (0.4 g, 47%).

Isomer **10b**: mp 119—120 °C (from CH_2Cl_2–hexane). $[\alpha]_{\mathrm{D}}^{30}$ −293.6° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 0.68 (3H, s), 0.78 (3H, s), 1.00 (3H, s), 1.05 (3H, s), 1.08—1.11 (1H, m), 1.14 (3H, s), 1.35 (3H, s), 1.57 (3H, d, J=1.2 Hz), 1.53—1.69 (4H, m), 1.65 (3H, d, J=1.2 Hz), 1.90—1.93 (2H, m), 3.14 (3H, s), 3.76 (1H, d, J=8.5 Hz), 4.36—4.38 (1H, m), 4.94 (1H, d, J=8.5 Hz). *Anal.* Calcd for $C_{25}H_{37}NO_3S$: C, 69.57; H, 8.64; N, 3.25. Found: C,69.41; H, 8.58; N, 3.18.

X-Ray Crystal Data for **10b**: $C_{25}H_{37}NO_3S$, orthorhombic, $P2_12_12_1$, a=11.459(1) Å, b=25.324(1) Å, c=8.303(1) Å, V=2409.4(4) Å^3, Z=4, μ(Cu$K\alpha$)=13.83 cm^{-1}, R=0.043.

Isomer **11b**: mp 114—115 °C (from CH_2Cl_2–hexane). $[\alpha]_{\mathrm{D}}^{31}$ +250.6° (c=0.98, $CHCl_3$). ^{1}H-NMR δ: 0.67 (3H, s), 0.77 (3H, s), 0.99 (3H, s), 1.05 (3H, s), 1.09—1.12 (1H, m), 1.14 (3H, s), 1.28 (3H, s), 1.57 (3H, d, J=1.2 Hz), 1.65 (3H, d, J=1.2 Hz), 1.60—1.63 (2H, m), 1.75—1.88 (3H, m), 2.23—2.27 (1H, m), 3.13 (3H, s), 3.75 (1H, d, J=8.5 Hz), 4.12—4.15 (1H, m), 5.15 (1H, d, J=8.5 Hz). *Anal.* Calcd for $C_{25}H_{37}NO_3S$: C, 69.57; H, 8.64; N, 3.25. Found: C,69.58; H, 8.73; N, 3.14.

(−)-1,7,8,9,10,10-Hexamethyl-3-thio-5-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-one (10c) Treatment of the diastereomer **10b** (1.0 g, 2.3 mmol) with $LiBH_4$ (9.2 mmol)–MeOH (0.7 ml) at 50 °C for 10 h gave the (−)-enantiomer **10c** as colorless crystals (0.5 g, 82%), mp 219—220 °C (from EtOH). $[\alpha]_{\mathrm{D}}^{31}$ −163.2° (c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57. Found: C, 66.71; H,8.55; N, 5.33.

(+)-1,7,8,9,10,10-Hexamethyl-3-thio-5-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-one (11c) Similar treatment of the *N*-MAC isomer **11b** (1.0 g, 2.3 mmol), as described above, gave the (+)-enantiomer **11c** (0.3 g, 60%) as colorless crystals, mp 218—219 °C (from EtOH). $[\alpha]_{\mathrm{D}}^{31}$ +162.0° (c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57. Found: C, 66.71; H,8.55; N, 5.33.

(−)-5-Propionyl-1,7-dimetyl-3-thio-5-aza-dibenzo[h,k]tricyclo-[5.2.2.0^{2,6}]undeca-8,10-dien-4-one (12) The lithium salts derived from **8c** (1,2 g, 3.9 mmol) and BuLi (4.3 mmol) in THF (39 ml), were treated with propionyl chloride (4.3 mmol) at −78 °C for 1 h and then at 0 °C for 2 h. The usual work-up followed by column chromatography on silica gel (CH_2Cl_2–hexane (3 : 7)) gave the *N*-butyryl derivative **12** (1.36 g, 95%) as colorless crystals, mp 170—171 °C (from hexane). $[\alpha]_{\mathrm{D}}^{30}$ −361.2° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 1.15 (3H, t, J=7.3 Hz), 1.84 (3H, s), 1.95 (3H, s), 2.73—2.86 (2H, m), 3.97 (1H, d, J=9.7 Hz), 5.00 (1H, d, J=9.7 Hz), 7.22—7.39 (8H, m). *Anal.* Calcd for $C_{22}H_{21}NO_2S$: C, 72.70; H, 5.82; N, 3.85. Found: C, 73.00; H, 5.88; N, 3.86.

(−)-5-Butyryl-1,7-dimethyl-3-thio-5-aza-dibenzo[h,k]tricyclo-[5.2.2.0^{2,6}]undeca-8,10-dien-4-one (13) Analogous to the above procedure, this compound was prepared from **8c** (0.8 g, 2.6 mmol) in 98% yield (0.99 g) as colorless crystals, mp 104—105 °C (from hexane). $[\alpha]_{\mathrm{D}}^{31}$ −356.6° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 0.97 (3H, t, J=7.3 Hz), 1.65—1.69 (2H, m), 1.84 (3H, s), 1.95 (3H, s), 2.67—2.84 (2H, m), 3.97 (1H, d, J=9.7 Hz), 5.01 (1H, d, J=9.7 Hz), 7.21—7.39 (8H, m). *Anal.* Calcd for $C_{23}H_{23}NO_2S$: C, 73.18; H, 6.14; N, 3.71. Found: C, 73.36; H, 5.99; N, 3.64.

(−)-5-Propionyl-1,7,8,9,10,10-hexamethyl-3-thio-5-azatricyclo-[5.2.1.0^{2,6}]dec-8- en-4-one (14) A solution of (−)-enantiomer **10c** (0.35 g, 1.3 mmol) and propionyl chloride (1.5 mmol) in CH_2Cl_2 (13 ml) was treated in the presence of triethylamine (4.1 mmol) at 0 °C for 1 h and then at 50 °C for another 1 h to give the *N*-butyryl derivative **14** (0.36 g, 85%) as colorless crystals, mp 55—56 °C (from hexane). $[\alpha]_{\mathrm{D}}^{28}$ −297.6° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 0.67 (3H, s), 0.79 (3H, s), 1.01 (3H, s), 1.09 (3H, s), 1.13 (3H, t, J=7.3 Hz), 1.50 (3H, d, J=1.2 Hz), 1.66 (3H, d, J=1.2 Hz), 2.77—2.82 (2H, m), 3.80 (1H, d, J=9.1 Hz), 4.99 (1H, d, J=9.1 Hz). *Anal.* Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.38; H, 8.23; N, 4.44.

(−)-5-Butyryl-1,7,8,9,10,10-hexamethyl-3-thio-5-azatricyclo-[5.2.1.0^{2,6}]dec-8- en-4-one (15) Analogous to the above procedure, this compound was prepared from **10c** (0.39 g, 1.5 mmol) in 86% yield (0.43 g) as colorless crystals, mp 78—79 °C (from hexane). $[\alpha]_{\mathrm{D}}^{28}$ −290.2° (c=0.50, $CHCl_3$). ^{1}H-NMR δ: 0.67 (3H, s), 0.79 (3H, s), 0.96 (3H, t, J=7.3 Hz), 1.01 (3H, s), 1.09 (3H, s), 1.50 (3H, d, J=1.2 Hz), 1.66 (3H, d, J=1.2 Hz), 1.64—1.67 (2H, m), 2.74—2.78 (2H, m), 3.80 (1H, d, J=9.1 Hz), 5.00 (1H, d, J=9.1 Hz). *Anal.* Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36. Found: C, 67.09; H, 8.59; N, 4.11.

General Procedure for Diastereoselective Alkylation To a solution of the *N*-propionyl or *N*-butyryl derivatives **12**—**15** (0.2 mmol) in THF (0.3 ml) was slowly added the base (1.05 eq), prepared *in situ* from hexamethyldisilazane (HMDS) and NaH or BuLi, under an atmosphere of Ar at −30 °C and, after standing for 1 h, alkyl halide was added. The mixture was treated with a saturated solution of NH_4Cl, and then extracted with AcOEt. The crude mixture of alkylated diastereomers thus obtained was directly analyzed by HPLC or capillary gas chromatography.

Absolute configulation of the alkylated adducts were determined as follows:

i) The benzylated products (R′=$PhCH_2$): the optical rotations ($[\alpha]_{\mathrm{D}}$ −10.3° (C_6H_6) from **8c** and $[\alpha]_{\mathrm{D}}$ −10.5° (C_6H_6) from **10c**) of 2-methyl-3-phenyl-1-propanol derived from reductive cleavage with $LiBH_4$–MeOH (1 : 2) were compared with the data previously reported ([lit., for (*S*)-form, $[\alpha]_{\mathrm{D}}$ −11.1° (C_6H_6)]).[14]

ii) The allylated products (R′=allyl): the authentic species were prepared from the 2-thiazolidinone auxiliaries and (2*R*)-2-methyl-4-propenoic acid.[14]

16 (HXN*=**8c**, R=Me, R′=allyl): ^{1}H-NMR δ: 1.05 (3H, d, J=6.7 Hz), 1.82 (3H, s), 1.95 (3H, s), 2.04—2.15 (1H, m), 2.53—2.60 (1H, m), 3.56—3.58 (1H, m), 3.97 (1H, d, J=9.7 Hz), 5.00 (1H, d, J=9.7 Hz), 5.09—5.14 (2H, m), 5.78—5.83 (1H, m), 7.22—7.39 (8H, m).

16 (HXN*=**10c**, R=Me, R′=allyl): ^{1}H-NMR δ: 0.67 (3H, s), 0.79 (3H, s), 1.01 (3H, s), 1.06 (3H, s), 1.07 (3H, d, J=6.7 Hz), 1.51 (3H, d, J=1.2 Hz), 1.66 (3H, d, J=1.2 Hz), 2.08—2.14 (1H, m), 2.50—2.56 (1H, m), 3.60—3.64 (1H, m), 3.79 (1H, d, J=9.1 Hz), 5.01 (1H, d, J=9.1 Hz), 5.03—

5.11 (2H, m), 5.72—5.79 (1H, m).

iii) The methylated products (R′=Me): the authentic samples were prepared from the 2-thiazolidinone auxiliaries and commercially available (2*S*)-2-methylbutyric acid.

16 (HXN*=**8c**, R=Et, R′=Me): ^{1}H-NMR δ: 0.85 (3H, t, *J*=7.9 Hz), 1.22 (3H, d, *J*=7.3 Hz), 1.34—1.37 (1H, m), 1.65—1.72 (1H, m), 1.83 (3H, s), 1.95 (3H, s), 3.38—3.40 (1H, m), 3.95 (1H, d, *J*=9.7 Hz), 5.06 (1H, d, *J*=9.7 Hz), 7.21—7.39 (8H, m).

16 (HXN*=**10c**, R=Et, R′=Me): ^{1}H-NMR δ: 0.67 (3H, s), 0.79 (3H, s), 0.86 (3H, t, *J*=7.3 Hz), 1.01 (3H, s), 1.08 (3H, s), 1.18 (3H, d, *J*=6.7 Hz), 1.33—1.39 (1H, m), 1.52 (3H, d, *J*=1.2 Hz), 1.67 (3H, d, *J*=1.2 Hz), 1.67—1.69 (1H, m), 3.41—3.45 (1H, m), 3.79 (1H, d, *J*=9.1 Hz), 5.01 (1H, d, *J*=9.1 Hz).

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