Asymmetric Synthesis of Functionalized Cyclopropanes via β-Lithiation–Cyclization of N-Monosubstituted 3-(Phenylthio)-2-[(phenylthio)methyl]propanamides

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Abstract: The reaction of *N*-[(1*R*,2*S*,3*R*,4*S*)-2-hydroxy-1,7,7-trimethylbicyclohept-3-yl]-3-(phenylthio)-2-[(phenylthio)-methyl]propanamide with 4 equiv of *n*-BuLi gives exclusively trans cyclopropanes in 94% yield (ratio of diastereomers 1:3). The use of the triisopropylsilyl ether of the amide led to high diastereoselectivity (ratio 1:11) in this cyclopropanation. The absolute configuration of the resulting diastereomeric cyclopropane was determined by X-ray crystallography. The β-lithiation and subsequent alkylation of the cyclopropanes provided a wide variety of optically pure cyclopropane derivatives.

A general synthetic approach to functionalized cyclopropanes with high optical purities would be of significant value not only because these cyclopropanes are frequently found in natural products[1] but also because they are synthetically useful intermediates for the construction of other chiral molecules.[2] Among the various methods reported, the Simmons–Smith reactions of chiral olefinic substances[1c,3] and the chiral carbenoid reaction of achiral alkenes[4] are highly effective procedures for the preparation of optically pure cyclopropanes. However, the asymmetric cyclopropanations, which additionally allow the formation of new chemical bonds, in particular carbon–carbon bonds, have not been described.[5]

We describe here a novel approach to the synthesis of chiral functionalized cyclopropane derivatives via β-lithiation[6]–cyclopropanation[7] of bis(β-phenylthio) carboxamides and subsequent alkylation of the resulting lithiocyclopropanes. Reaction of *N*-[(1*R*,2*S*,3*R*,4*S*)-2-hydroxy-1,7,7-trimethylbicyclohept-3-yl]-3-(phenylthio)-2-[(phenylthio)methyl]propanamide (**1a**) with 4 equiv of *n*-BuLi at −78 °C for 10 min and at 0 °C for 3 h gave a mixture of trans isomers of cyclopropanes in 94% yield (ratio of the diastereomers 1:3). These cyclopropanes were readily separated by flash chromatography on silica gel.[8] The absolute configuration of the less mobile diastereomer **3**, obtained as a crystalline solid, was determined by X-ray crystallography (Figure 1; Scheme I).

The use of the *tert*-butyldimethylsilyl ether of amide **1a** led to better diastereoselectivity in this cyclopropanation. Thus, addition of 3 equiv of *n*-BuLi to **1b** followed by desilylation with tetrabutylammonium fluoride produced (1*S*,2*R*)-**2** and (1*R*,2*S*)-**3** in 84% overall yield from **1a** as a 1:5.2 mixture of diastereomers. It is important to note that the hydroxy function on the bicyclic moiety of the amide is necessary for chromatographic separation of the diastereomers,[8] since with the other chiral amines such as (*R*)-(+)-α-methylbenzylamine or (*R*)-(+)-1-(1-naphthyl)ethylamine the separation of the diastereomers was impossible and the chemical yields of the cyclopropanes were 70–80%. When amide **1c** bearing the triisopropylsilyl group as a control element[9] was used in this sequence, the highest degree of diastereoselectivity (1:11 ratio) was achieved (85% overall yield from **1a**). Molecular models indicate the triisopropylsilyl group causes nonbonding interaction to restrict rotation about C_1–C_2 bond and covers the front face of the amide moiety. Thus, addition of *n*-BuLi to **1c** approaches from the back side of the amide group to remove the *pro-S* proton selectively, resulting in the predominant formation of (1*R*,2*S*)-**3**.

Removal of the chiral auxiliary from cyclopropane (1*S*,2*R*)-**2** was achieved by N-*tert*-butoxycarbonylation[10] followed by methanolysis or by hydrolysis and subsequent amidation to afford (1*S*,2*R*)-**4** in 73% yield ($[\alpha]^{23}_{D}$ −56.9° (*c* 1.26, MeOH)) or (1*S*,2*R*)-**5** in 52% overall yield ($[\alpha]^{25}_{D}$ −79.0° (*c* 0.80, dioxane)), respectively. Diastereomer (1*R*,2*S*)-**3** was converted under

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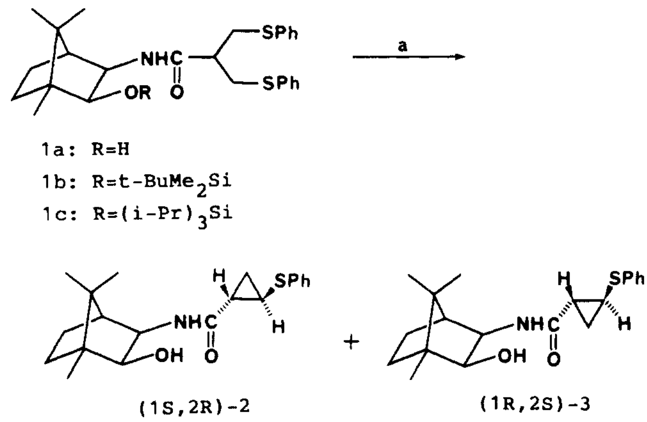
Scheme I[a]



[a] **1a**, 4 equiv of *n*-BuLi, THF; **1b** and **1c**, 3 equiv of *n*-BuLi and then 2 equiv of *n*-Bu_4NF.

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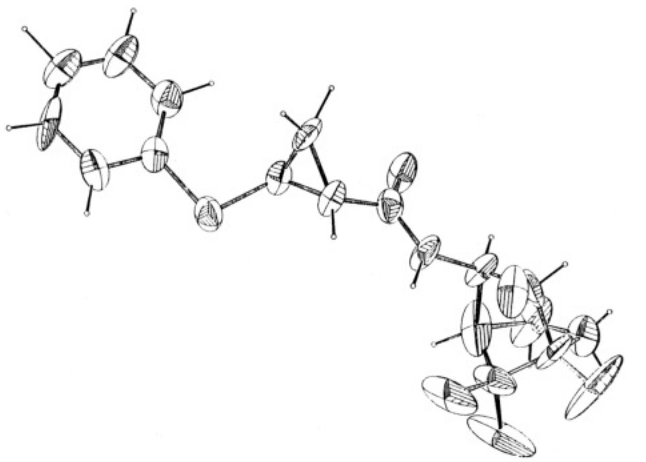
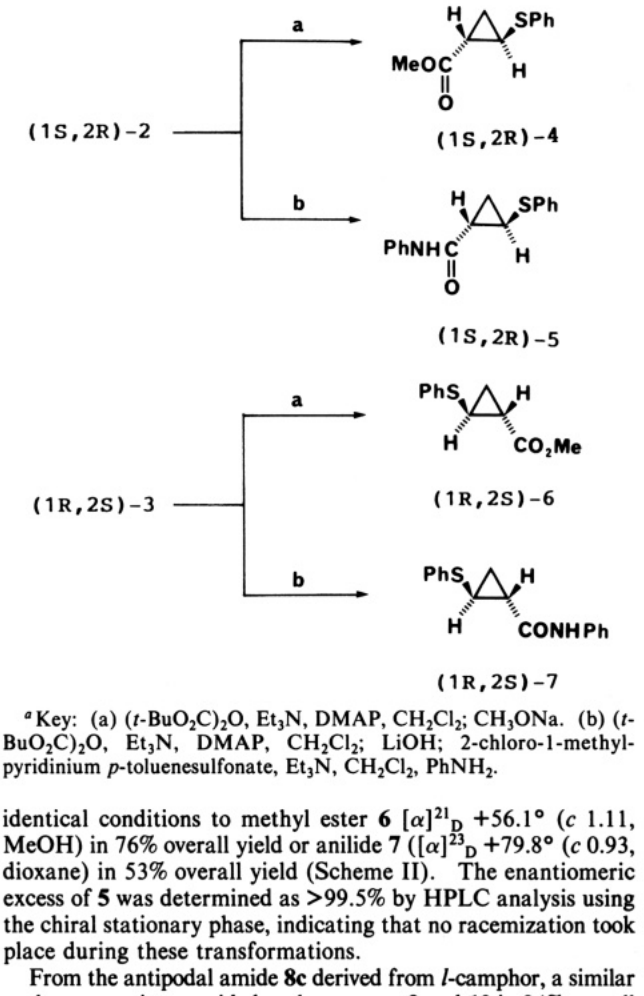


Figure 1. X-ray structure of cyclopropane (1*R*,2*S*)-3.

Scheme II[a]

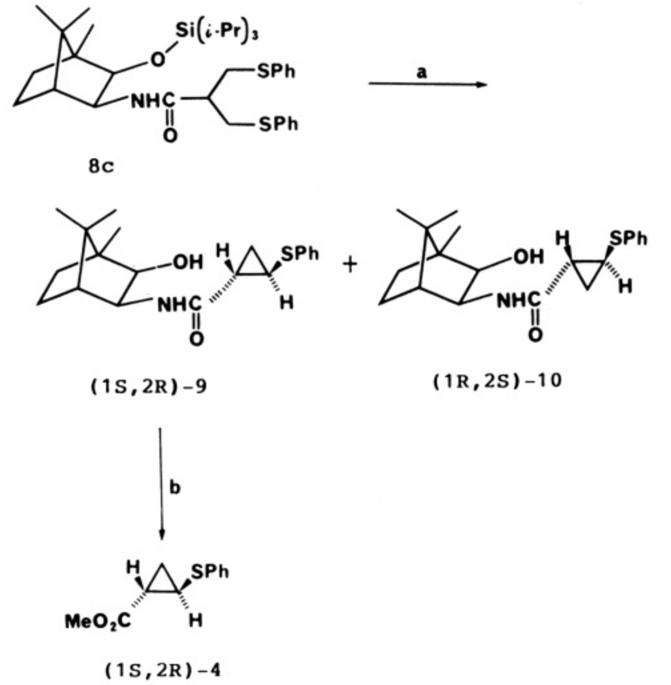


[a] Key: (a) (t-$BuO_2C)_2O$, Et_3N, DMAP, CH_2Cl_2; CH_3ONa. (b) (t-$BuO_2C)_2O$, Et_3N, DMAP, CH_2Cl_2; LiOH; 2-chloro-1-methylpyridinium p-toluenesulfonate, Et_3N, CH_2Cl_2, $PhNH_2$.

identical conditions to methyl ester **6** $[\alpha]^{21}_D$ +56.1° (*c* 1.11, MeOH) in 76% overall yield or anilide **7** ($[\alpha]^{23}_D$ +79.8° (*c* 0.93, dioxane) in 53% overall yield (Scheme II). The enantiomeric excess of **5** was determined as >99.5% by HPLC analysis using the chiral stationary phase, indicating that no racemization took place during these transformations.

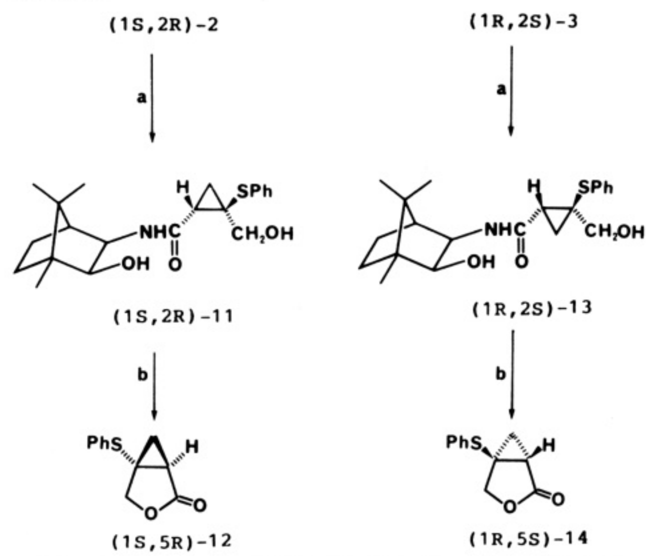
From the antipodal amide **8c** derived from *l*-camphor, a similar cyclopropanation provided cyclopropanes **9** and **10** in 84% overall yield with a 12:1 diastereoselectivity (Scheme III). The absolute configuration of product **9** was determined as (1*S*,2*R*)-**9** by transformation of **9** into methyl 2-(phenylthio)cyclopropanecarboxylate, exhibiting a rotation of $[\alpha]^{26}_D$ −59.2° (*c* 1.14, MeOH) in satisfactory agreement with that of (1*S*,2*R*)-**4** ($[\alpha]^{23}_D$ −56.9° (*c* 1.26, MeOH)) prepared from (1*S*,2*R*)-**2**.

Scheme III[a]



[a] Key: (a) 3 equiv of n-BuLi; 2 equiv of n-Bu_4NF. (b) (t-$BuO_2C)_2O$, Et_3N, DMAP, CH_2Cl_2; CH_3ONa.

Scheme IV[a]



[a] Key: (a) 3 equiv of n-BuLi, THF; $(CH_2O)_n$. (b) 10% HCl, dioxane, reflux.

Treatment of the pure diastereomer (1*S*,2*R*)-**2** with 3 equiv of *n*-BuLi in THF at −78 °C produced yellow solution of the trianion. Addition of paraformaldehyde gave **11** in 44% yield, which upon acidic hydrolysis produced (1*S*,5*R*)-3-oxa-5-(phenylthio)bicyclo[3.1.0]hexan-2-one (**12**) ($[\alpha]^{23}_D$ +89.2° (*c* 1.00, dioxane)) in 72% yield. Reaction of (1*R*,2*S*)-**3** under identical conditions gave **13** in 61% yield, which was cyclized to enantiomeric lactone **14** ($[\alpha]^{23}_D$ −86.8° (*c* 1.16, dioxane) in 60% yield (Scheme IV).

It should be emphasized that the three-step procedure—triisopropylsilylation, cyclopropanation, and desilylation—provides cyclopropanes in high overall yields with high diastereoselectivity.

(5) The carbon–carbon bond formation of the lithiocyclopropane obtained by resolution of [2-(tributylstannyl)cyclopropyl]methanol has been reported, see: Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415.

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(8) When (*R*)-(+)-α-methylbenzylamine was used as a chiral auxiliary, the diastereoselectivity was low (ratio 1:1.7).

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Since both enantiomers of bis(β-phenylthio) carboxamides are readily available, either isomer of the cyclopropanes can be synthesized in high optical purity. Further studies on the enantioselective substitutions of chiral lithiocyclopropanes, as well as applications in other chiral molecules of interest, are in progress.

Experimental Section

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclohept-3-yl]-3-(phenylthio)-2-[(phenylthio)methyl]propanamide (1a).** A solution of 3-(phenylthio)-2-[(phenylthio)methyl]propionyl chloride (prepared from 3-(phenylthio)-2-[(phenylthio)methyl]propionic acid and $SOCl_2$ in dry benzene) in dry THF (40 mL) was added dropwise with magnetic stirring to a solution of 3-*exo*-amino-2-*exo*-hydroxybornane[11] (6.09 g, 0.036 mol, ca. 90% purity) and triethylamine (5.52 mL, 0.0396 mol) in THF (60 mL) at 0 °C under argon. The mixture was allowed to warm to room temperature overnight. Dilute HCl (30 mL) was added, and the mixture was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated. Chromatography (silica, hexane–ethyl acetate (5:1)) gave a crude amide as a solid (15.15 g). The solid was dissolved in hot hexane–ethyl acetate (2.5:1, 350 mL) and cooled at room temperature to give a mixture of *endo*- and *exo*-amide (2.93 g, ratio 47:53 by HPLC). The filtrate was concentrated, the residual white solid was dissolved in hot hexane–ethyl acetate (4:1, 250 mL), and the solution was filtered and cooled at room temperature to give pure *exo*-amide **1a** (>99.5% by HPLC) in 43% yield (7.08 g): mp 94.5–95.5 °C; $[\alpha]^{24}_D$ +13.8° (*c* 1.07, dioxane); IR (KBr) 3250, 2940, 1640, 1510, 760 cm^{-1}; ^1H NMR δ 0.80, 0.93, 1.03 (s, 9 H), 1.03 (m, 2 H), 1.49 (m, 1 H), 1.63–1.73 (m, 2 H), 2.10 (br s, 1 H), 2.47 (m, 1 H), 3.18 (m, 4 H), 3.75 (m, 2 H), 6.10 (m, 1 H), 7.26 (m, 10 H). Anal. Calcd for $C_{26}H_{33}NOS_2$: C, 68.53; H, 7.30; N, 3.07. Found: C, 68.50; H, 7.35; N, 2.96.

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1,7,7-trimethylbicyclohept-3-yl]-3-(phenylthio)-2-[(phenylthio)methyl]propanamide (1b).** The *tert*-butyldimethylsilylation was carried out according to a literature method.[9] To a solution of **1a** (1.20 g, 2.63 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C under argon were added *tert*-butyldimethylsilyl triflate[9] (0.72 mL, 3.42 mmol) and 2,6-lutidine (0.61 mL, 5.26 mmol). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the dropwise addition of 2% HCl (3 mL). Brine was added, and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were washed with dilute HCl, saturated aqueous $NaHCO_3$, and brine and dried (Na_2SO_4). Evaporation of the solvent followed by chromatography (silica, hexane–ethyl acetate (10:1)) gave 1.45 g of **1b** (97%) as a crystalline material: mp 70–71 °C; $[\alpha]^{22}_D$ −32.0° (*c* 1.08, dioxane); IR (KBr) 2920, 1680, 1490, 750 cm^{-1}; ^1H NMR δ −0.15 (s, 3 H), 0.00 (s, 3 H), 0.58 (s, 9 H), 0.75 (s, 3 H), 0.79 (s, 3 H), 1.01 (s, 3 H), 0.87–1.93 (m, 5 H), 2.39 (m, 1 H), 3.21 (d, J = 7.0 Hz, 4 H), 3.55–3.80 (m, 2 H), 6.19 (d, J = 5.0 Hz, 1 H), 7.12–7.29 (m, 10 H). Anal. Calcd for $C_{32}H_{47}NO_2SiS_2$: C, 67.43; H, 8.31, N, 2.46. Found: C, 67.66; H, 8.33; N, 2.43.

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-[(Triisopropylsilyl)oxy]-1,7,7-trimethylbicyclohept-3-yl]-3-(phenylthio)-2-[(phenylthio)methyl]propanamide (1c).** By a similar procedure, the triisopropylsilyl ether was prepared in 100% yield (2.69 g) after column chromatography (silica, hexane–ethyl acetate (10:1)) from amide **1a** (2.00 g, 4.39 mmol) and triisopropylsilyl triflate[9] (1.41 g, 5.27 mmol): mp 67–67.5 $[\alpha]^{22}_D$ −34.0° (*c* 1.01, dioxane); IR (KBr) 2930, 1660, 1485, 755, 710 cm^{-1}; ^1H NMR δ 0.79 (s, 3 H), 0.87 (d, J = 5.5 Hz, 8 H), 0.90 (s, 3 H), 0.96 (s, 13 H), 1.06 (s, 3 H), 1.16 (dt, J = 4.0, 8.5 Hz, 1 H), 1.48 (dt, J = 4.0, 12.0 Hz, 1 H), 1.68 (m, 1 H), 1.97 (d, J = 4.3 Hz, 1 H), 2.46 (q, J = 6.9 Hz, 1 H), 3.19–3.31 (m, 4 H), 3.78 (m, 1 H), 3.99 (d, J = 7.9 Hz, 1 H), 6.27 (d, J = 5.8 Hz, 1 H), 7.12–7.32 (m, 10 H). Anal. Calcd for $C_{35}H_{53}NO_2SiS_2$: C, 68.69; H, 8.73; N, 2.29. Found: C, 68.61; H, 8.79; N, 2.34.

Cyclopropanation of 1a. To a stirred solution of amide **1a** (1.00 g, 2.19 mmol) in dry THF (60 mL) at −78 °C under argon was added *n*-BuLi (8.76 mmol). The mixture was stirred for 15 min at −78 °C and for 3 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (3 mL), poured into H_2O, and extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (silica, hexane–ethyl acetate (5:1)) gave 0.18 g (23%) of (1*S*,2*R*)-**2** and 0.54 g (71%) of (1*R*,2*S*)-**3**.

(1*S*,2*R*)-*N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclohept-3-yl]-2-(phenylthio)cyclopropanecarboxamide (2): mp 127 °C; $[\alpha]^{18}_D$ +32.2° (*c* 1.00, dioxane); IR (KBr) 3270, 2940, 1630, 1510, 1070, 755 cm^{-1}; ^1H NMR δ 0.80 (s, 3 H), 0.93 (s, 3 H), 1.08 (s, 3 H), 0.83–1.79 (m, 8 H), 2.47 (br s, 1 H), 2.64 (m, 1 H), 3.75 (s, 1 H), 3.79 (s, 1 H), 6.36 (br s, 1 H), 7.01–7.25 (m, 5 H). Anal. Calcd for $C_{20}H_{27}NO_2S$: C, 69.53; H, 7.88; N, 4.05. Found: C, 69.46; H, 7.85; N, 4.05.

(1*R*,2*S*)-*N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclohept-3-yl]-2-(phenylthio)cyclopropanecarboxamide (3): mp 113.5–115 °C; $[\alpha]^{22}_D$ −2.26° (*c* 0.98, dioxane); IR (KBr) 3350, 2940, 1645, 1510, 1080, 760 cm^{-1}; ^1H NMR δ 0.83 (s, 3 H), 0.93 (s, 3 H), 1.05 (m, 1 H), 1.09 (s, 3 H), 1.10–1.20 (m, 2 H), 1.51 (dt, J = 4.0, 12.0 Hz, 1 H), 1.62-1.79 (m, 3 H), 1.88 (d, J = 4.6 Hz, 1 H), 2.49 (br s, 1 H), 2.73 (m, 1 H), 3.76–3.82 (m, 2 H), 6.54 (br s, 1 H), 7.14 (m, 1 H), 7.21–7.30 (m, 4 H). Anal. Calcd for $C_{20}H_{27}NO_2S$: C, 69.53; H, 7.78; N, 4.05. Found: C, 69.35; H, 7.89; N, 3.92.

General Procedure for Cyclopropanation of 1b and 1c. To a stirred solution of amide **1c** (1.50 g, 2.45 mmol) in dry THF (30 mL) at −78 °C under argon was added *n*-BuLi (7.35 mmol). The mixture was stirred for 10 min at −78 °C and for 3 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (3 mL), poured into H_2O, and extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated. This material was dissolved in dry THF (20 mL), and tetrabutylammonium fluoride (4.90 mmol) was added. The mixture was stirred for 2 h at room temperature and quenched with brine (3 mL). The reaction mixture was poured into H_2O and extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$, dilute HCl, and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (silica, hexane–ethyl acetate (5:1)) gave 0.06 g (7%) of (1*S*,2*R*)-**2** and 0.67 g (79%) of (1*R*,2*S*)-**3**.

Methyl (1*S*,2*R*)-2-(Phenylthio)cyclopropanecarboxylate (4). The conversion of (1*S*,2*R*)-**2** into the corresponding methyl ester was carried out according to a literature procedure.[10] To a solution of **2** (0.29 g, 0.84 mmol) in dry CH_2Cl_2 (9 mL) under argon were added 4-(dimethylamino)pyridine (0.15 g, 1.26 mmol) and triethylamine (0.18 mL, 1.26 mmol). A solution of di-*tert*-butyl dicarbonate (1.57 g, 7.18 mmol) in dry CH_2Cl_2 (3 mL) was added and the resultant solution stirred for 1 h. The solvent was evaporated and the crude product purified by chromatography (silica, hexane–ethyl acetate (5:1)) to give 0.36 g (94%) of the *N*-Boc derivative as a colorless solid. This material (0.49 g, 1.10 mmol) was dissolved in dry MeOH (4 mL), and sodium methoxide (1.2 mL, 2M in MeOH) was added. After the mixture was stirred for 4.5 h at room temperature, brine (20 mL) was added. The product was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to give a pale yellow oil. The crude ester was chromatographed (silica, hexane–ethyl acetate (10:1)) to give 0.23 g (78%) of **4** as a pale yellow oil: bp 95–98 °C (0.2 mmHg); $[\alpha]^{23}_D$ −56.9° (*c* 1.26, MeOH); IR (thin film) 1735, 1445, 1390, 1210, 1180 cm^{-1}; ^1H NMR δ 1.24 (m, 1 H), 1.66 (m, 1 H), 1.92 (m, 1 H), 2.78 (m, 1 H), 3.73 (s, 3 H), 7.16–7.34 (m, 5 H); MS, *m/e* 208 (M^+).

(1*S*,2*R*)-*N*-Phenyl-2-(phenylthio)cyclopropanecarboxamide (5). The conversion of (1*S*,2*R*)-**3** into the corresponding anilide **5** was carried out according to a literature method.[10] To a solution of *N*-*tert*-butoxycarbonyl amide (0.50 g, 1.12 mmol) of **2** in dry THF (7.5 mL) was added a 1.0 M solution of lithium hydroxide (4.4 mL). The mixture was stirred overnight at room temperature. The reaction mixture was acidified by 10% HCl to pH 1 and extracted with CH_2Cl_2 (4 × 20 mL). The organic layer was back-extracted with 15% NaOH (4 × 10 mL). The alkaline solution was acidified by 10% HCl to pH 1, and the product was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave 0.19 g (86%) of (1*S*,2*R*)-2-(phenylthio)cyclopropanecarboxylic acid as a white solid. The acid was converted to **5** by using 2-chloro-1-methylpyridinium *p*-toluenesulfonate[12] as a condensing agent. The crude amide was purified by chromatography (silica, hexane–ethyl acetate (5:1)) to give **5** (77%) as a crystalline material (>99.5% ee by HPLC): mp 166.5–168 °C; $[\alpha]^{25}_D$ −79.0° (*c* 0.80, dioxane); IR (KBr) 3270, 1650, 1600, 1540, 1450, 755, 705 cm^{-1}; ^1H NMR δ 1.21 (m, 1 H), 1.74–1.78 (m, 2 H), 2.85 (m, 1 H), 7.08–7.50 (m, 10 H), 7.63 (br s, 1 H). Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.35; H, 5.61; N, 5.20. Found: C, 71.48; H, 5.69; N, 5.13.

(1*S*,2*R*)-*N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclohept-3-yl]-2-(hydroxymethyl)-2-(phenylthio)cyclopropanecarboxamide (11). To a solution of (1*S*,2*R*)-**2** (0.60 g, 1.74 mmol) in dry THF (30 mL) at −78 °C under argon was added *n*-BuLi (5.71 mmol) dropwise. The reaction mixture was stirred for 10 min at −78 °C followed by 1.5 h at 0 °C. Paraformaldehyde (0.08 g, 2.61 mmol, dried under vacuum) was added and the resulting suspension stirred for 18 h. The reaction was quenched by saturated aqueous NH_4Cl (3 mL), and H_2O (30 mL) was

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added. The product was extracted with ethyl acetate (3 × 30 mL), and the combined extracts were washed with dilute HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), evaporated, and chromatographed (silica, hexane–ethyl acetate (2:1)) to give 0.29 g (44%) of **11** and starting amide **2** (43% recovery): mp 116.5–117 °C; $[\alpha]^{23}{}_D$ −37.9° (*c* 0.99, dioxane); IR (KBr) 3300, 2940, 1620, 1515, 755 cm^{-1}; ^1H NMR δ 0.81 (s, 3 H), 0.92 (s, 3 H), 1.09 (s, 3 H), 0.81–2.17 (m, 8 H), 3.10 (br s, 1 H), 3.74–4.21 (m, 6 H), 6.50 (d, *J* = 6.0 Hz, 1 H), 7.20–7.47 (m, 5 H).

(1*S*,5*R*)-3-Oxa-5-(phenylthio)bicyclo[3.1.0]heptan-2-one (12). To a solution of (1*S*,2*R*)-**11** (0.29 g, 0.77 mmol) in 1,4-dioxane (8 mL) was added 10% HCl (8 mL). The mixture was warmed to reflux for 1 h under argon and allowed to cool. The solvent was evaporated, and the residue was diluted with brine and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude residue was chromatographed (silica, hexane–ethyl acetate (5:1)) to give 0.12 g (72%) of **12** as a colorless oil: bp 153 °C (0.7 mmHg); $[\alpha]^{23}{}_D$ +89.2° (*c* 1.00, dioxane); IR (thin film) 1780, 1480, 1185, 1030, 760, 705 cm^{-1}; ^1H NMR δ 1.45 (m, 1 H), 1.75 (m, 1 H), 2.37 (m, 1 H), 4.32 (d, *J* = 3.0 Hz, 2 H), 7.17–7.44 (m, 5 H); MS, *m/e* 206 (M^+).

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Supplementary Material Available: Model and tables of final atomic positional parameters and isotropic thermal parameters, bond distances, and bond angles for the crystal structure of (1*R*,2*S*)-**3**, and physical and spectral data for compounds **6**, **7**, **8a**, **8c**, **9**, **10**, **4**, **13**, and **14** (13 pages). Ordering information is given on any current masthead page.

Five-Membered Aromatic Heterocycles as Dienophiles in Diels–Alder Reactions. Furan, Pyrrole, and Indole

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Abstract: Isoprene is shown to undergo high-yielding cycloaddition with β-acylfurans and N-benzenesulfonylated β-acylpyrroles and β-acylindoles and 1,3-butadiene with the latter. Except for the reactions catalyzed by aluminum trichloride they show poor regioselectivity. The Diels–Alder adducts of N-benzenesulfonylated β-nitropyrrole and β-nitroindole suffer from thermal nitrous acid extrusion and by *p*-quinone oxidation can be converted into indoles and carbazoles, respectively.

It has been known for some time, that aromatic heterocycles such as furan (**1a**), thiophene (**1b**), and pyrrole (**1c**) undergo Diels–Alder reactions despite their aromaticity and hence expected inertness. In view of their electron-rich constitution and elec-

1a, Y = O 2a, R = Me 3 4
b, Y = S b, R = H
c, Y = NH

tron-donor properties they have been involved mostly as the diene component in the cycloaddition process. Thus, furans have been used efficiently in this capacity since the early days of the Diels–Alder reaction.[1] The much lower reactivity of the thiophenes has prevented their frequent use as Diels–Alder dienes.[2] Finally, whereas pyrroles initially were shunned as cycloaddition substrates in view of the formation of α-alkylpyrroles on their exposure to dienophiles,[3] they were shown later to be efficient Diels–Alder dienes when N-substituted by electron-withdrawing groups.[4]

There exists a limited number of examples of five-membered, aromatic heterocycles acting as dienophiles in Diels–Alder reactions, although in 8 of the 10 cases, a special driving force permits expression of such unusual heterocycle behavior—the cycloaddition requiring inverse electron demand (electron-poor diene reacting with an electron-rich dienophile)[5] or being constrained to an intramolecular, unidirectional process.[6] One of the two examples of an intermolecular Diels–Alder reaction (with normal electron demand) of an aromatic heterocycle of type **1** on record is the formation of 2:1 adduct **4** on thermal reaction of 1,3-butadiene (**2b**) with furfural (**3**).[7] Even this case is unusual, insofar as the reaction leads to something other than a 1:1 adduct and was carried out under specialized conditions intended to imitate the extractive distillation of unreacted butadiene with furfural solvent in industrial plants of synthetic rubber production. Nevertheless, this observation constitutes the first indication of the feasibility of normal Diels–Alder chemistry with five-membered, aromatic heterocycles, holding electron-withdrawing groups, as dienophiles. As the following discussion illustrates, this heterocycle reaction tendency could be translated into a new method of organochemical synthesis.

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