Doubly Bridged S-Heterocyclic Ethylenes via Stereospecific [2,3] Sigmatropic Rearrangement. Avenue to Short-Bridged Betweenanenes[1]

Vanda Cerè, Claudio Paolucci, Salvatore Pollicino, Edda Sandri,* and Antonino Fava*

Istituto di Chimica Organica, Università di Bologna, 40136 Bologna, Italy

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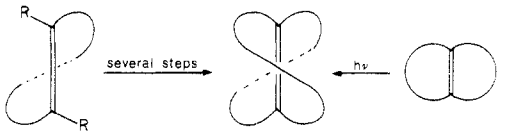
"Cis" and "trans" doubly bridged S-heterocyclic ethylenes result by stereospecific [2,3] sigmatropic rearrangement of, respectively, cis and trans isomers of spirocyclic sulfonium ylides (eq 1 and 2). This approach has been applied to ylides derived from 7-methylene-1-thiaspiro[5,11]heptadecane (**2**), leading to derivatives of "*cis*"- and "*trans*"-15-thiabicyclo[10.7.0]nonadec-1(12)-enes **5** and **6**. The latter is a "thiabetweenanene",[2a] whose short (seven atom) bridge was further shortened by sulfur extrusion via a Ramberg–Bäcklund variant.[16] Hydrogenation of the Ramberg–Bäcklund product diene, **9**, gave a [10.6]betweenanene derivative, **10**. The approach appears to be uniquely suitable for the synthesis of short-bridged betweenanenes.

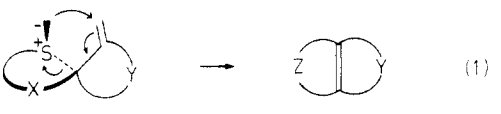
Bis(*trans*-polymethylene)ethylenes (I), or betweenanenes,[2] first recognized as a structural class by Cahn, Ingold, and Prelog,[3] have been recently synthesized by Marshall's[2] and by Nakazaki's[4] groups. Marshall's approach involves first the synthesis of a *trans*-cycloalkene (II) carrying a



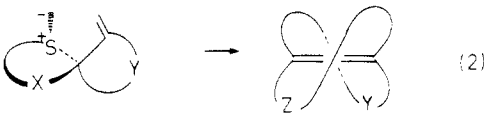
II I III

group (R) at the two open olefinic positions that could be further elaborated and made to cyclize. Thus, in the first synthesis of [10.10]betweenanene, cyclization was achieved via acyloin condensation[2a] and in the second, considerably shortened and improved synthesis,[2b] via the McMurry Ti(O) procedure.[5] Nakazaki's synthesis simply consists of the photoisomerization of the isomeric "cis" doubly bridged ethylene (III).[4] This synthesis has been recently modified so as to obtain an optically active sample of [8.8]betweenanene, albeit with a minimal enantiomeric excess.[4c]

Because of the unique chemical and physical properties which "trans" doubly bridged ethylenes may have [the double bond is essentially inaccessible and highly unreactive, and the molecules are chiral though they may have high symmetry (up to the D_2 symmetry group)], new synthetic approaches are desirable, particularly if they can extend the scope of the existing ones. In this paper we report a novel strategy to both "cis" and "trans" doubly bridged ethylenes, the key feature of which is the introduction of the double bond in the required position and geometry by way of a stereospecific sigmatropic rearrangement. The example we describe here features a [2,3] sigmatropic rearrangement of a sulfonium ylide, which results in shifting a double bond from an exocyclic to an adjacent spirocyclic position (eq 1 and 2). The configuration of the double bond in the product appears to be controlled by the geometry of the starting ylide, "cis" and



(1)



(2)

"trans" doubly bridged ethylenes resulting from cis and trans ylides, respectively (eq 1 and 2). Since one of the two product bridges results from a sulfonium ylide rearrangement, such a bridge contains a sulfide function. It is conceivable, however, that the approach may be extended to other sigmatropic processes (e.g., Cope) which would give homocyclic doubly bridged ethylenes. In any case, the scope of our synthesis may be furthered by extrusion of the sulfur atom from the heterobridge, leading to the next lower carbocyclic homologue. A successful attempt in this direction is described in which a [10.6]-betweenanene derivative was produced. Since a six-atom bridge is most likely the shortest attainable,[6,7] our method appears to be uniquely apt to synthetizing short-bridged betweenanenes.

Results and Discussion

As shown in eq 1 and 2, the synthetic approach requires, in the key step, an allylic sulfonium ylide derived from a spiro sulfide having at positions adjacent to the quaternary carbon the heteroatom in one ring and an exocyclic methylene in the other. Such a structure can be built from a cycloalkanone by spirocyclization at one of the α carbons, the methylene grouping being eventually created by a Wittig reaction.

For testing the feasibility of the approach, we selected conditions which would facilitate its success. Thus, cyclododecanone was chosen, which, beside being easily available and inexpensive, has the advantage of providing a strainless ten-membered bridge in the final product. The

(1) For a preliminary account of part of this work see: Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Chem. Soc., Chem. Commun.* **1980**, 755.

(2) (a) Marshall, J. A.; Lewellyn, M. *J. Am. Chem. Soc.* **1977**, *99*, 3508. (b) Marshall, J. A.; Chung, K. H. *J. Org. Chem.* **1979**, *44*, 1566.

(3) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

(4) (a) Nakazaki, M.; Yamamoto, K.; Yanagi, J. *J. Chem. Soc., Chem. Commun.* **1977**, 346; (b) *J. Am. Chem. Soc.* **1979**, *101*, 147. (c) Nakazaki, M.; Yamamoto, K.; Maeda, M. *J. Chem. Soc., Chem. Commun.* **1980**, 294.

(5) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255.

(6) The strain of a betweenanene molecule is related to, and probably very close to, the strain of the shortest *trans*-cycloalkene moiety it contains. Since *trans*-cyclooctene is the smallest *trans*-cycloalkene capable of durable existence,[7] [6.6]betweenanene is predictably the smallest stable betweenanene.

(7) (a) Cope, A. C.; Pike, R. A.; Spencer, C. F. *J. Am. Chem. Soc.* **1953**, *75*, 3212. (b) Corey, E. J.; Carey, F. A.; Winter, R. A. E. *Ibid.* **1965**, *87*, 934. (c) For a recent review, see: Greenberg, A.; Liebman, J. F. "Strained Organic Molecules"; Academic Press: New York, 1978, Chapter 3.

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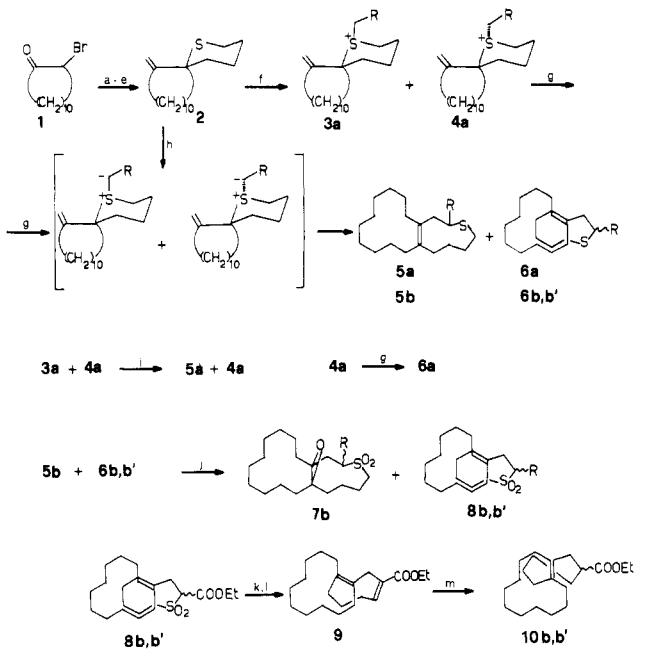
Scheme I



[a] a, R = H; b, R = COOEt. [b] (a) $HO(CH_2)_4SH$, KOH, EtOH, 10 °C, 63%; (b) TsCl, Pyr, 88%; (c) LiBr, acetone, 82%; (d) NaH, DME, reflux, 5 h, 30%; (e) Ph_3PCH_2, Me_2SO, 57 °C, 3 days, 86.7%; (f) $CF_3SO_3CH_3$, CH_2Cl_2, 96%; (g) 1.1 equiv of *t*-BuOK, THF/*t*-BuOH (10/1 v/v), −40 °C, 90%; (h) N_2CH_2COOEt, $CuSO_4$, PhH, 58%; (i) same as in g except 0.5 equiv of *t*-BuOK and −70 °C; (j) MCPBA, CH_2Cl_2, room temperature; (k) NaH, C_2Cl_6, DME, room temperature; (l) *t*-BuOK, DME, room temperature (64%, overall for steps k and l); (m) H_2/Pd (63%).

second bridge was projected to be a seven-atom one, although this size was expected to introduce some strain,[8,9] because of the anticipated advantage of having to close a six-membered ring in the spirocyclization step. The synthetic sequence is outlined in Scheme I.

Steps a–c and e were straightforward. The spirocyclization step, d, was found to give low yields under a variety of solvent, base, and temperature conditions. The least unsatisfactory results were obtained by using dimethoxyethane solvent at reflux and NaH as the base. More systematic work would be necessary to improve this step. The methylation step, f, gave a 1:1 mixture of isomeric sulfonium salts, **3a** and **4a** (R = H), whose configurations could be unambiguously assigned by ^1H NMR. The two isomers have their SCH_3 singlet at δ 2.70 (**3a**) and 3.00 (**4a**) and may be assigned the cis and trans structure, respectively, on the basis of previous evidence that in *S*-methyl sulfonium salts derived from 2-vinylthiacycloalkanes (five–seven membered) the methyl singlet of the cis isomer is shielded by 0.15–0.25 ppm with respect to the trans isomer. The assignment is consistent with the chemical behavior of **3a** and **4a**: when their equimolar mixture was treated at −40 °C with 1 equiv of *t*-BuOK (step g) to form the corresponding mixture of methylides (Scheme I), a product was isolated which consisted of a 1:1 mixture of the isomeric "cis" (**5a**) and "trans" (**6a**) doubly bridged ethylenes. However, when the reaction progress was monitored (GLC and NMR), **3a** appeared to disappear faster than **4a**, while **5a** was formed faster than **6a**. Following this cue, we sought conditions under which **3a** would react selectively. When the equimolar mixture of **3a** and **4a** was treated at −70 °C with 0.5 equiv of potassium *tert*-butoxide (step i) the product consisted solely of **5a** which could be easily separated from unreacted **4a**. The latter, treated again with base at −40 °C, gave essentially pure **6a**. Thus, the rearrangement appears to be stereospecific, the "cis" (**5a**) and "trans" (**6a**) doubly bridged ethylenes arising by rearrangement of the methylides formed, respectively, from the cis (**3a**) and trans (**4a**) sulfonium salts.[10,11]

The physical and chemical properties of the isomeric doubly bridged ethylenes **5a** and **6a** are consistent with the geometrical assignment. In the ^1H NMR spectra, the protons α to sulfur give rise in both isomers to a multiplet near δ 2.1. Apart from this feature, however, the spectra (for details see the Experimental Section) resemble very closely those reported for the "cis" and "trans" isomer of the [8.8] doubly bridged ethylene.[4b] In the ^{13}C NMR spectra, **6a** has the olefinic carbons farther apart (δ 135.7 and 131.7) than those in **5a** (δ 135.4 and 133.3) while the aliphatic carbons are generally more downfield in **6a** (from δ 38.4 to 24.4) than in **5a** (from δ 32.2 to 22.2), as expected for a trans–cis pair of cyclic olefins.[9a,12,13] Finally, the geometrical assignment is confirmed by the reactivity toward *m*-chloroperbenzoic acid: while **5a** gives a sulfone epoxide (**7a**), **6a** resists epoxidation, yielding the unsaturated sulfone **8a** (see Experimental Section).

The rearrangement was carried out also with a carbethoxy-stabilized ylide. This was prepared in situ by thermal Cu(II)-catalyzed decomposition of ethyl diazoacetate[14] in the presence of spiro sulfide **2** (step h; R = COOEt). The product consisted of three isomers in an ~3:2:1 ratio. The major isomer appears to be the "cis" doubly bridged ethylene **5b**, while the other two are diastereoisomers of the substituted "trans" doubly bridged ethylene, **6b** and **6b′**.[15] (Apparently, the cis and trans ylides are formed in an ~1:1 ratio in the carbene reaction also.)

To test the possibility of further shortening the seven-atom bridge by sulfur extrusion, we chose to apply a Ramberg–Bäklund catalytic hydrogenation sequence to the isomeric mixture of carbethoxy derivatives **6b,b′**. This choice was suggested by Vedejs' finding that (1*Z*,4*E*)-2-carbethoxycyclooctadiene may be obtained in high yield by a Ramberg–Bäcklund variant from (*E*)-2-carbethoxythiacyclonon-4-ene.[16] To this end the mixture of oxidation products was column chromatographed to separate **7b** from **8b,b′**. The latter, treated with NaH and hexachloroethane (step k), formed a mixture of diastereomeric α-carbethoxy α-chloro sulfones which, when treated with potassium *tert*-butoxide (step l), gave the Ramberg–Bäcklund product, (1*RS*)-14-carbethoxybicyclo[10.6.0]octadeca-1(12),14-diene (**9**). Catalytic hydrogenation of **9**

(8) To a first approximation, a seven-atom chain should cause a strain on the order of that in *trans*-cyclononene (i.e., ~14 kcal/mol).[7c]

(9) (a) Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* **1978**, *43*, 4826; (b) *Ibid.* **1979**, *44*, 4128.

(10) The steric course of the ring enlargement of cyclic six-membered sulfonium ylides by sigmatropic rearrangement may be rationalized in terms of ground-state conformational factors in accord with an early transition state.[9b,11]

(11) Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A., to be submitted for publication.

(12) Cerè, V.; Pollicino, S.; Sandri, E.; Fava, A. *J. Am. Chem. Soc.* **1978**, *100*, 1516.

(13) Stothers, J. B. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1972; p 69.

(14) Ando, W.; Kondo, S.; Nakayama, K.; Ichibori, K.; Kohoda, H.; Yamato, H.; Imai, I.; Nakaido, S.; Migita, T. *J. Am. Chem. Soc.* **1972**, *94*, 3870. Ando, W.; Yamada, M.; Matzusaki, E.; Migita, T. *J. Org. Chem.* **1972**, *37*, 3791.

(15) For R ≠ H, compounds of structure **6** have two elements of chirality, a plane, due to the conformationally fixed trans double bond, and a center (C_{14}, the carbon carrying the substituent). As such they exist as diastereomeric pairs.

(16) Vedejs, E.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4884.

(step m) gave an ~2:1 mixture of diastereomeric (*RS,SR*)- and (*RR,SS*)-14-carbethoxybicyclo[10.6.0]octadec-1(12)-enes (**10b,b'**).

No attempt was made to separate the diastereoisomers of **10** or to establish their relative configuration. The presence of the carboxyl group to be eventually removed may provide a useful handle for optical resolution. This goal is being actively pursued in this laboratory, along with the synthesis of short-bridged betweenanenes (the [6.6] member in particular) for which our approach has proven to be uniquely suitable.

Experimental Section

Proton NMR spectra were recorded at 100 MHz on a Varian XL-100 operating in the CW mode. Proton-noise-decoupled ^{13}C spectra were recorded at 25.15 MHz with a Varian XL-100 by the Fourier transform technique; single-frequency, off-resonance spectra were obtained by irradiation at δ −4 in the proton spectrum. Unless otherwise stated, ^1H and ^{13}C shifts are given in parts per million from Me_4Si in $CDCl_3$ solvent. GLC analyses were carried out with a Hewlett–Packard 5700 instrument equipped with a flame-ionization detector ($^1/_8$ in. × 3 m columns, 10% and 7% C 20 M on Chromosorb WHP).

Solvents and reagents were obtained dry as follows. Methylene chloride, *tert*-butyl alcohol, and benzene were distilled from calcium hydride; dimethyl sulfoxide was distilled from calcium hydride at reduced pressure [bp 64 °C (4 mm)]. Tetrahydrofuran and dimethoxyethane distilled from sodium and calcium hydride, respectively, were redistilled from $LiAlH_4$ prior to use.

All melting points are uncorrected, and the yields are for isolated products.

7-Methylene-1-thiaspiro[5.11]heptadecane (2) was obtained from the corresponding 7-oxo derivative by the modification of the Wittig reaction employing methylsulfinyl carbanion–dimethyl sulfoxide.[17] A solution of sodium methylsulfinyl carbanion was prepared under nitrogen from 0.1 mol of sodium hydride and 50 mL of dry Me_2SO.[18] To this solution was added 35.7 g (0.1 mol) of methyltriphenylphosphonium bromide in 90 mL of warm Me_2SO. After the mixture was stirred at room temperature for 15 min, 10.7 g (0.04 mol) of 7-oxo-1-thiaspiro[5.11]heptadecane in 30 mL of THF was added and stirring continued for 3 days at 57 °C. The resulting yellow solution was poured into 400 mL of water, and the aqueous phase (containing some precipitated triphenylphosphine oxide) was extracted with pentane (4 × 100 mL). The combined extracts, after being dried and evaporated, yielded 12 g of a crude product. Separation by column chromatography (SiO_2, eluant benzene) yielded unreacted starting material (second eluted fraction; 0.92 g, 8.6%) and the title compound [first eluted fraction, 8.5 g, 86.7% (accounting for recovered starting material)]: mp 56–57 °C (EtOH); ^1H NMR δ 5.47 and 5.22 (2 br s, W_H = 3.0 and 4.0 Hz, 1 H each, $=CH_2$), 2.5 (m, 2 H, allylic H's), 2.1 (m, 2 H, SCH_2), 1.9–0.9 (m, 24 H); ^{13}C NMR δ 145.6 (>C=), 113.7 ($=CH_2$), 53.6 (C_6), 37.3 and 36.9 (C_2 and C_8 interchangeable), 27.4, 26.7, 26.5, 26.3, 24.6, 23.2, 22.5, 22.4, 22.2, 22.0, 19.1 (unassigned).

Anal. Calcd for $C_{17}H_{30}S$: C, 76.62; H, 11.34. Found: C, 76.71; H, 11.28.

7-Oxo-1-thiaspiro[5.11]heptadecane was obtained by spirocyclization (Krapcho procedure)[19] of 4-bromobutyl 2-oxocyclododecyl sulfide. A solution of the latter (21.8 g, 0.0625 mol) in 80 mL of dimethoxyethane was added dropwise under stirring to a refluxing slurry of NaH (3 g after being freed from oil, 0.125 mol) in 80 mL of dimethoxyethane. The reaction mixture was refluxed for 5 h, ice cooled, and quenched with water. The mixture was then poured into 700 mL of water and pentane extracted to afford, after drying and removal of solvent, 11 g of crude product. This material, separated by column chromatography (SiO_2, eluant benzene), yielded one major component (5 g) along with a trace of starting material (0.3 g) and three unidentified minor components (1.5 g, overall). [Further elution with benzene–methanol and methanol gave a mixture of unidentified polar products (3.5 g).] The major component proved to be the title compound (30%): mp 78–79 °C (EtOH); ^1H NMR δ 3.16 (ddd, J = 18.0, 12.0, 3.0 Hz, 1 H, one of the protons on C_5 located in the deshielding cone of the C=O group), 2.5 (m, 4 H, CH_2S and CH_2CO), 2.0–1.1 (large m with a narrow band emerging at 1.28, 23 H); ^{13}C NMR δ 211.6 (CO), 57.5 (C_6), 37.3, 33.9, 33.2, 28.0, 26.6 (2 C), 26.5, 23.7, 22.8, 22.5, 22.3, 22.1, 21.9, 19.9 (unassigned).

Anal. Calcd for $C_{16}H_{28}OS$: C, 71.58; H, 10.51. Found: C, 71.46; H, 10.64.

4-Bromobutyl 2-Oxocyclododecyl Sulfide. A mixture of 44 g (0.1 mol) of crude 4-(tosyloxy)butyl 2-oxocyclododecyl sulfide, 16.4 g (0.2 mol) of lithium bromide, and 380 mL of acetone (distilled from K_2CO_3) was refluxed under stirring for 45 min. The cooled mixture was filtered from the precipitated lithium tosylate which was washed with acetone. The combined acetone solutions were evaporated in vacuo at room temperature to give a mixture of the bromo derivative, residual lithium tosylate, and excess lithium bromide. This mixture was extracted under stirring with pentane (5 × 200 mL). The combined pentane extracts were dried, concentrated in vacuo at room temperature to ca. 50–60 mL, and then cooled at −10 °C. The crystallized 4-bromobutyl 2-oxocyclododecyl sulfide was filtered off and washed with cooled pentane: 28.6 g (82%); mp 55–56 °C; ^1H NMR δ 3.45 (m, 3 H, CH_2Br and SCH), 2.71 (m, 2 H, CH_2CO), 2.45 (t, 2 H, SCH_2), 2.1–1.2 (m with a narrow band emerging at 1.32, 22 H).

Anal. Calcd for $C_{16}H_{29}BrOS$: C, 55.00; H, 8.37. Found: C, 55.03; H, 8.31.

4-(Tosyloxy)butyl 2-Oxocyclododecyl Sulfide. *p*-Toluenesulfonyl chloride (22.9 g, 0.12 mol) was added to a solution of crude 4-hydroxybutyl 2-oxocyclododecyl sulfide (32.5 g, 0.114 mol) in 115 mL of freshly distilled pyridine cooled at 8–10 °C. The mixture, after being stirred for 30 min at 10 °C, was allowed to stand for 14 h at 0 °C and then poured into water (700 mL). The precipitated crude tosylate was filtered off, washed with water, and dried in vacuo (44 g, 88%; mp 60–64 °C). This material (90% pure by NMR) was used without further purification because crystallization from EtOH resulted in extensive reaction leading to cyclized thiolanium salt. For purposes of characterization, a sample of purified 4-hydroxybutyl 2-oxocyclododecyl sulfide was reacted as described above to give a pure tosylate: mp 67–68 °C; ^1H NMR δ 7.57 (AB q, J = 9.0 Hz, $\Delta\nu$ = 42 Hz, 4 H, aromatic H's), 4.03 (t, 2 H, CH_2O), 3.42 (q, J = 10.5 and 3.0 Hz, 1 H, SCH), 2.68 (m, 2 H, CH_2CO), 2.46 (s, 3 H, CH_3), 2.37 (t, 2 H, SCH_2), 2.0–1.1 (m with narrow band emerging at 1.32, 22 H).

Anal. Calcd for $C_{23}H_{36}O_4S_2$: C, 62.69; H, 8.23. Found: C, 62.61; H, 8.25.

4-Hydroxybutyl 2-Oxocyclododecyl Sulfide. To a ethanolic solution of 2-bromocyclododecanone[20] (44.4 g, 0.17 mol in 200 mL) cooled at 8–10 °C was added dropwise over 30 min a solution of 4-hydroxybutanethiol[21] (18.0 g, 0.17 mol) in 200 mL of 0.85 M ethanolic KOH. Reaction occurred immediately, and after the addition was complete, the mixture was cooled at 0 °C and the precipitated sodium bromide filtered off. The filtrate was evaporated, and the residue was distilled under reduced pressure [bp 190–198 °C (0.6 mm)] to yield 30.6 g [63%, >90% pure (^{13}C NMR)] of a yellow waxy solid. This product was used without further purification; an analytical sample was obtained by column chromatography (SiO_2, eluant 6% EtOH–$CHCl_3$): bp 192 °C (0.6 mm); ^1H NMR δ 3.64 (m, 2 H, CH_2O), 3.46 (q, J = 11.0 and 3.5 Hz, 1 H, SCH), 2.71 (m, 2 H, CH_2CO), 2.44 (m, 2 H, SCH_2), 2.1–1.1 (m, from which the hydroxyl H emerges at 1.64 and a narrow band at 1.32, 23 H overall); ^{13}C NMR δ 209.2 (CO), 61.8 (CH_2O), 51.8 (SCH), 36.0, 31.8, 30.0, 29.9, 25.8, 25.4, 25.0, 24.7, 24.4 (2 C), 24.2, 22.8, 22.3 (unassigned).

Anal. Calcd for $C_{16}H_{30}O_2S$: C, 67.08; H, 10.56. Found: 67.12; H, 10.59.

***cis*- and *trans*-1-Methyl-7-methylene-1-thioniaspiro[5.11]heptadecane Trifluoromethansulfonates (Triflates) (3a and 4a).** To a solution of **2** (0.84 g, 3.16 mmol) in 5 mL of CH_2Cl_2 at −5 °C was added methyl trifluoromethansulfonate (0.573 g, 3.47 mmol), and the mixture was stirred for 3 h at 0 °C. The

(17) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.
(18) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 866.
(19) Krapcho, A. P.; McCullough, J. E. *J. Org. Chem.* **1967**, *32*, 2453.
(20) Ziegenbein, W. *Chem. Ber.* **1961**, *94*, 2989.
(21) Harding, J. S.; Owen, L. N. *J. Chem. Soc.* **1954**, 1536.

solvent was removed in vacuo, and the residue was washed with 50% ether–pentane (3 × 4 mL). Repeated attempts failed to crystallize the oily salt (1.3 g, 96%), which appears to be a ca. 1:1 mixture of diastereomers. Metathesis to the hexafluorophosphate salt with aqueous NH_4PF_6 gave a solid (mp 128–135 °C) whose isomer distribution was the same as that of the triflate salt and which did not change on crystallization from ethanol. The trans isomer **4a** (95% pure) could be obtained, however, by recovering the unreacted sulfonium salt after rearrangement of the **3a–4a** mixture with 0.5 equiv of *t*-BuOK (see below). The **4a** isomer has the following: ^{1}H NMR δ 5.52 (m, 2 H, $=CH_2$), 3.7–3.1 (m, 2 H, CH_2S), 3.00 (s, 3 H, CH_3), 2.3–1.0 (large m with a narrow band emerging at 1.30, 26 H); ^{13}C NMR δ 140.8 (>C=), 117.3 ($=CH_2$), 65.0 (C_6), 33.6 and 32.8 (C_2 and C_8 interchangeable), 28.3, 26.9, 26.0, 25.3, 23.8, 22.9, 21.9, 21.8, 21.4, 19.6, 18.2, 16.9, 15.2 (unassigned).

The mixture of **3a** and **4a** has essentially the same ^{1}H NMR features as **4a** except that the SCH_3 protons appear as two singlets of nearly equal intensity at δ 3.00 and 2.70. From the spectrum of the mixture of **3a** and **4a** the following ^{13}C resonances of **3a** have been obtained: δ 141.7 (C=), 119.7 ($=CH_2$), 63.6 (C_6), 32.2, 28.2, 25.8 (2 C), 24.7, 24.2, 23.5, 22.6, 22.4, 21.9, 19.7, 18.2, 16.3, 15.8 (unassigned).

Rearrangement of 3a and 4a: C_s- and (1*RS*)-15-Thiabicyclo[10.7.0]nonadec-1(12)-enes (5a and 6a). (A) With an Excess of Base. A solution of 300 mg (0.7 mmol) of a 1:1 mixture of **3a** and **4a** (see above) in 6 mL of THF–*t*-BuOH (10:1) was treated at −40 °C with 1.2 equiv of *t*-BuOK. After 2 h at −40 °C, the mixture was quenched with water and pentane extracted. Removal of solvent gave an oily residue (184 mg, 94%) consisting (GLC) of a mixture of two isomeric sulfides (both *m/e* 280) in a ca. 1:1 ratio.

(B) With a Deficit of Base. A solution of 1.3 g (3 mmol) of a 1:1 mixture of **3a** and **4a** in 23 mL of THF–*t*-BuOH (10:1) was treated at −70 °C with ~0.5 equiv (171 mg, 1.52 mmol) of *t*-BuOK. After 2 h at −70 °C and 30 min at −20 °C, the mixture was poured into 10 mL of water. After extraction with pentane to remove the sulfide fraction, the aqueous phase was extracted with CH_2Cl_2 to recover the unreacted sulfonium salt (550 mg) which appeared to be the isomer **4a** (95% pure). After removal of the solvent, the pentane extract gave 430 mg of the isomeric sulfide with the longer retention time, **5a** (mp 48–49 °C after crystallization from ethanol).

Rearrangement of the recovered **4a** (550 mg, 1.28 mmol) with 1.2 equiv of *t*-BuOK at −40 °C for 2 h gave the isomeric sulfide **6a**: 340 mg (95%); mp 42–43 °C (EtOH). The isomeric double-bridged ethylenes have the following characteristics. For **5a**: ^{1}H NMR δ 2.7–2.3 (m, 8 H, allylic H's), 2.2–2.0 (m, 4 H, CH_2SCH_2), 1.7–1.2 (m, from which emerges an intense narrow band at 1.40, 20 H); ^{13}C NMR δ 135.4 and 133.3 (olefinic carbons), 32.2, 31.4, 30.3, 28.8, 28.6, 26.5, 26.1, 26.0, 25.6, 25.3, 25.2, 24.5, 24.4, 24.1, 23.2, 22.2 (unassigned). For **6a**: ^{1}H NMR δ 3.0–2.1 (complex m, 12 H overall, allylic and α to sulfur H's), 1.8–1.1 (large m from which an intense narrow band emerges at 1.26, 20 H); ^{13}C NMR δ 135.7 and 131.7 (olefinic carbons), 38.4, 36.2, 33.6, 33.1, 33.0, 31.8, 28.2, 27.6, 26.4, 26.2, 26.1, 26.0, 24.9, 24.8, 24.6, 24.4 (unassigned).

1,12-Epoxy-15-thiabicyclo[10.7.0]nonadecane 15,15-Dioxide (7a). To a solution of *m*-chloroperbenzoic acid (MCPBA) [340 mg (85%), 1.68 mmol] in 5 mL of CH_2Cl_2 cooled at 5 °C was added the sulfide 5a (148 mg, 0.53 mmol) dissolved in CH_2Cl_2 (1 mL). After being allowed to stand 3 h at room temperature, the reaction mixture was extracted with 10% aqueous Na_2SO_3 and 10% aqueous Na_2CO_3.

Removal of the solvent gave 160 mg (92%) of crude **7a**: mp 191–192 °C (MeOH); mass spectrum, *m/e* 328; ^{13}C NMR 68.8 and 68.2 (C_1 and C_{12} interchangeable), 50.3 and 49.9 (C_{14} and C_{16} interchangeable); the remaining resonances are comprised between δ 27.9 and 20.6.

Anal. Calcd for $C_{18}H_{32}O_3S$: C, 65.81; H, 9.82. Found: C, 65.77; H, 9.79.

Oxidation under identical conditions of the sulfide mixture of **5a** and **6a** gave a mixture of **7a** and **8a** (see below), which could be separated by column chromatography (SiO_2, eluant $CHCl_3$).

C_s-15-Thiabicyclo[10.7.0]nonadec-1(12)ene 15,15-Dioxide. To a solution of MCPBA [204 mg (85%), 0.1 mmol] in 5 mL of CH_2Cl_2 cooled at −10 °C was added the sulfide **5a** (140 mg, 0.5 mmol) in CH_2Cl_2 (1 mL). After 2 h at −10 °C, workup as above gave 140 mg (90%) of crude dioxide contaminated by the same epoxide **7a**. Crystalization from EtOH gave pure dioxide: mp 165–166 °C; ^{13}C NMR δ 134.7 and 133.3 (olefinic carbons), 53.3 and 50.5 (C_{14} and C_{16} interchangeable); the remaining carbons resonate between δ 27.9 and 19.1.

Anal. Calcd for $C_{18}H_{32}O_2S$: C, 69.18; H, 10.32. Found: C, 69.15; H, 10.37.

(1*RS*)-15-Thiabicyclo[10.7.0]nonadec-1(12)-ene 15,15-Dioxide (8a). Oxidation of sulfide **6a** under the conditions reported above for the preparation of **7a** gave the dioxide **8a** in 92% yield; mp 101–102 °C. The double bond was found to be equally unaffected under more severe conditions (MCPBA in refluxing benzene for 20 h): ^{13}C NMR δ 136.5 and 132.0 (olefinic carbons), 60.2 and 56.5 (C_{14} and C_{16} interchangeable); the remaining resonances are comprised between δ 33.9 and 19.5.

Anal. Calcd for $C_{18}H_{32}O_2S$: C, 69.18; H, 10.32. Found: C, 69.11; H, 10.29.

Reaction of Spiro Sulfide 2 with N_2CH_2COOEt. Mixture of (14*RS*)- and Diastereomeric [1,14-(*RS,SR*)]- and [1,14-(*RR,SS*)]-14-Carbethoxy-15-thiabicyclo[10.7.0]nonadec-1-(12)-enes (5b and 6b,b′). A mixture of spiro sulfide **2** (2.66 g, 0.01 mol), ethyl diazoacetate (2.28 g, 0.02 mol), and dry $CuSO_4$ (0.2 g) in 10 mL of dry benzene was heated at 40–45 °C under nitrogen. Gas evolution started immediately, and the temperature was maintained at 50–55 °C by intermittent external cooling. After the exothermic reaction had subsided, the reaction mixture was maintained at 50 °C for 20 min by external heating, cooled, and filtered. After removal of the solvent, the oily residue was column chromatographed (SiO_2, eluant benzene) to give the spiro sulfide **2** as first-eluted material (0.97 g, 36.5%) and a second-eluted product which proved to be a mixture of the three isomeric sulfides **5b** and **6b,b′** [1.3 g, 58% (accounting for recovered **2**)]. The ^{1}H NMR absorption of the ethyl group methylene appears as three very closely spaced quartets at δ 4.2, indicating three isomers are present. The more abundant isomer (the "cis" isomer; see below) displays a quartet at δ 3.62 (J = 12.0 and 6.0 Hz, intensity ~$^1/_2$ H, $C_{14}H$). The presence of three isomers was confirmed by the ^{13}C spectrum which showed three carbonyl and six olefinic carbon singlets, whose relative intensities are roughly in a 1:2:3 ratio. The more abundant isomer (CO at δ 172.6) has the olefinic carbons closest together (δ 135.3 and 132.6) and is assigned the "cis" structure **5b** (see also below). The next most abundant [δ 173.5 (CO), 137.4, and 130.1 (olefinic carbons)] and the least abundant isomers (δ 172.9, 139.2, and 128.3) are the diastereoisomers of the 14-substituted "trans" doubly bridged ethylene, **6b,b′**.

Oxidation of the 5b and 6b,b′ Mixture: 1,12-Epoxy-14-carbethoxy-15-thiabicyclo[10.7.0]nonadecane 15,15-Dioxide and Diastereomeric [1,14-(*RS-SR*)]- and [1,14-(*RR,SS*)]-14-Carbethoxy-15-thiabicyclo[10.7.0]nonadec-1(12)-ene 15,15-Dioxides (7b and 8b,b′). Oxidation with 3 equiv of MCPBA of the sulfide mixture of **5b** and **6b,b′** (2.5 g, 7.1 mmol) under the conditions reported for **7a** gave a mixture of sulfone epoxide **7b** and sulfones **8b,b′**, which were separated by column chromatography (SiO_2, eluant 10% ethyl acetate–dichloromethane). The fraction eluted first (1.57 g 57.6%; mp 113–118 °C) appears to contain two isomers in a ca. 4:1 ratio, each characterized by two olefinic ^{13}C singlets: δ 137.4, 130.9 (major); 140.4, 127.5 (minor). The fact that the double bond has resisted epoxidation proves the two products to be the diastereoisomer of the "trans" doubly bridged ethylene sulfone **8b,b′**. Other significant ^{13}C resonances are (major isomer first) δ 165.7 and 165.4 (CO), 71.6 and 70.0 (C_{14}), 62.8 and 62.4 (OCH_2), 62.4 and 61.5 (C_{16}). The remaining resonances are comprised between δ 35.6 and 14.0.

Anal. Calcd for $C_{21}H_{36}O_4S$: C, 65.59; H, 9.44. Found: C, 65.49; H, 9.48.

The fraction eluted second [0.68 g, 24%; mp 138–139 °C (MeOH)] is made up of the sulfone epoxide **7b**: ^{1}H NMR δ 4.34 (q, J = 7.5 Hz, 2 H, OCH_2), 4.10 (q, J = 7.5 and 5.0 Hz, 1 H, $C_{14}H$), 3.68–.2.52 (complex m's, 4 H overall, $C_{16}H_2$ and $C_{13}H_2$), 2.3–1.2 (m, 29 H). The ^{13}C NMR indicates that only one of two possible isomers of **7b** is present and suggests that it has the trans structure. This assignment is justified insofar as the cis structure would imply epoxidation from the side of the carbethoxy group in a highly

congested transition state. The ^{13}C NMR spectrum shows the following: δ 165.7 (CO), 69.2 and 67.1 (C_1 and C_{12} interchangeable), 66.3 (C_{14}), 63.0 (OCH_2), 50.6 (C_{16}); the remaining resonances are comprised between δ 29.8 and 14.0.

Anal. Calcd for $C_{21}H_{36}O_5S$: C, 62.97; H, 9.06. Found: C, 62.89; H, 8.96.

Ramberg-Bäcklund Rearrangement of 8b,b′: (1*RS*)-14-Carbethoxybicyclo[10.6.0]octadeca-1(12),14-diene (9). A solution of **8b,b′** (1.14 g, 2.97 mmol) in 14 mL of DME was added dropwise at room temperature to a stirred suspension of NaH (180 mg after being freed from oil, 7.5 mmol) in 13 mL of DME. The mixture was then ice cooled, and a solution of hexachloroethane (844 mg, 3.56 mmol) in 6 mL of DME was added. The ice bath was removed and the stirring continued for 14 h at room temperature. The reaction mixture, resulting in a white precipitate, was cautiously quenched with 20% aqueous NH_4Cl, poured into 20 mL of water, and extracted with CH_2Cl_2. After removal of the solvent, TLC analysis of the residue revealed no less than three products, which were separated by column chromatography (SiO_2, eluant 3% ethyl acetate-benzene). The first-eluted material (70 mg, 7.3%) proved to be the diene **9**, while the last-eluted fraction consisted of unreacted **8b,b′** (60 mg, 5.2%). On the basis of ^{13}C NMR, the major product (915 mg, 73.8%) appears to consist of two isomeric chloro sulfones in a ca. 1.2:1 ratio. [The relevant ^{13}C singlets are (more abundant isomer first) δ 165.0 and 166.3 (CO), 142.5, 126.8 and 143.4, 126.0 (olefinic carbons), and 89.2 and 86.6 (C_{14}). The last two resonances are particularly significant as they can only be compatible with the α-carbon carrying a chlorine as well as carbethoxy substituent.] It appears that the reaction stops at the α-chloro α-carbethoxy α′-sodio sulfone stage, which precipitates out and, in this form, is unable to undergo the Ramberg-Bäcklund reaction. Analogous results were obtained when the reaction was carried out with 3.5 equiv of NaH for 24 h; however, an effective conversion could be achieved by treatment of the recovered chloro sulfones (915 mg, 2.19 mmol) dissolved in 40 mL of DME with *t*-BuOK (240 mg, 2.6 mmol) for 2 h at room temperature. Water-dichloromethane workup and separation as described above gave 240 mg of unreacted chloro sulfone and 390 mg of diene **9** [overall yield 460 mg (64%, based on the reacted **8b,b′**)]. No further attempt was made to optimize the reaction. In the ^1H NMR spectrum the olefinic proton at δ 6.75 shows up as a triplet, further split to a quartet by long-range allylic couplings (J = 2.5 and 1.5 Hz) with the protons at δ 3.76 and 2.77. These are the diallylic protons at C_{13} and give rise to an AB quartet (J = 19.0, $\Delta\nu$ = 99 Hz). (The spacing of the olefinic H triplet corresponds to 7.5 Hz. Since, however, the H's on C_{16} to which the olefinic H is coupled are magnetically unequivalent, it is dubious that the 7.5-Hz spacing is meaningful in terms of coupling constants. Most likely this is a case of a deceptively simple ABX spectrum and arises because the AB protons are very nearly isochronous. Since, however, the AB part is not discernible, the question remains unsettled.) The remaining protons (29) occur between δ 2.6 and 1.0, the CH_3 triplet being at δ 1.29: ^{13}C NMR δ 168.8 (CO), 141.3 (C_{15}), 138.5, 137.8 and 133.5 (C_1, C_{12}, and C_{14} interchangeable), 60.4 (OCH_2), 36.0, 33.9, 32.7, 32.3, 27.8, 26.7, 26.5, 26.1, 25.5, 25.4, 25.2, 24.9, 24.7 (2 c, unassigned), 14.4 (CH_3).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.24; H, 10.69.

[1,14-(*RS,SR*)]- and [1,14-(*RR,SS*)]-14-Carbethoxybicyclo[10.6.0]octadec-1(12)-enes (10b,b′). An ethanolic solution of diene **9** (150 mg, 0.47 mmol, in 15 mL of ethanol) containing 260 mg of 10% Pd/C was hydrogenated at room temperature and at a pressure of 3 atm of H_2 for 12 h. Filtration and removal of solvent gave essentially pure **10** (95 mg, 63%) as a mixture of two diastereoisomers in a ca. 2:1 ratio. The ^1H NMR spectrum shows no olefinic absorption but shows two ethyl quartets at δ 4.16 and 4.12 (major): the remaining absorption is complex absorption from δ 3.0 to 1.2, whose only discernible feature is the major methyl triplet at δ 1.25. The ^{13}C spectrum has the following signals (major isomer first): δ 175.9 and 176.3 (CO), 138.8 and 139.3 (C_1), 133.3 and 134.9 (C_{12}), 60.2 (CH_2O, both isomers), 51.0 and 48.9 (C_{14}), 14.3 (CH_3, both isomers). The remaining resonances are comprised between δ 36.9 and 24.2.

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.61; H, 11.35.

Registry No. **1**, 31236-94-9; **2**, 75700-50-4; **3a**, 75700-52-6; **4a**, 75700-54-8; **5a**, 75700-55-9; (±)-**5b**, 75700-56-0; (±)-**6a**, 75700-57-1; (±)-**6b**, 75764-62-4; (±)-**6b′**, 75764-63-5; **7a**, 75700-58-2; **7b**, 75700-59-3; C_s-**8a**, 75700-60-6; 1(*RS*)-**8a**, 75700-61-7; (±)-**8b**, 75700-62-8; (±)-**8b′**, 75764-64-6; (±)-**8b** α-chloro derivative, 75700-63-9; (±)-**8b′** α-chloro derivative, 75765-39-8; (±)-**9**, 75700-64-0; (±)-**10b**, 75700-65-1; (±)-**10b′**, 75764-65-7; 7-oxo-1-thiaspiro[5.11]heptadecane, 75700-66-2; 4-bromobutyl 2-oxocyclodecyl sulfide, 75700-67-3; 4-(tosyloxy)butyl 2-oxocyclododecyl sulfide, 75716-20-0; 4-hydroxybutyl 2-oxocyclododecyl sulfide, 75700-68-4; 4-hydroxybutanethiol, 14970-83-3.

Intramolecular *O,N*-Acyl Transfer via Cyclic Intermediates of Nine and Twelve Members. Models for Extensions of the Amine Capture Strategy for Peptide Synthesis

D. S. Kemp,* Daniel J. Kerkman, See-Lap Leung, and Gunnar Hanson

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Rate constants are reported for the intramolecular *O,N*-acyl-transfer reactions of 2-amino-*N*-benzyl-*N*-[2-(acyloxy)-4-nitrobenzyl]acetamides, 2-amino-*N*-benzyl-*N*-[(4-acetoxy-5-xanthyl)methylene]acetamide, ethyl *N*-(2-acetoxybenzyl)-2-aminoacetate, methyl *N*-[(8-acetoxy-1-naphthyl)methylene]-2-aminoacetate and their alanine and valine analogues in acetonitrile, Me_2SO, and other solvents. Synthesis of these substrates is described, and a novel two-step synthesis is reported of 4-hydroxy-5-formylxanthene from 2,3-diacetoxybenzaldehyde and 2-(isopropoxymethylene)cyclohexanone in 29% yield. Facile intramolecular acyl transfer via cyclic intermediates of 9 and 12 members is described, and steric and solvent effects on rates of acyl transfer are reported for these processes and compared with those for other intra- and intermolecular acyl-transfer reactions. The significance of these results for amide formation by amine capture is discussed.

Previously, we have outlined an amine capture strategy for amide bond formation (Scheme I) and have proposed a working example, the 4-methoxy-3-(acyloxy)-2-hydroxybenzaldehydes, which react with primary amines to form Schiff bases in the capture step.[1] We have also described failures to realize rapid intramolecular *O,N*-acyl transfer in a variety of structures which were intended as

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