(85%); mp 228–229 °C. Anal. Calcd C, 61.9; H, 3.3; Cl, 25.0; N, 9.8. Found: C, 61.6; H, 3.3; Cl, 25.0; N, 9.9. The ^{1}H NMR spectrum [$CDCl_3$, Me_4Si; δ 7–8.1 (m, 13 H, aromatics), 6.3 (br, 1 H, NH)] is consistent with the one reported for the unsubstituted arylpyridazine.[23]

X-ray Analysis. Crystals of **1a** ($C_{22}H_{16}NO_2$) are monoclinic: space group $P2_1/n$, a = 21.229 (5) Å, b = 13.632 (6) Å, c = 5.972 (8) Å; β = 94.1 (6)°, Z = 4, d_c = 1.26 g/cm^3, d_o = 1.24 g/cm^3. A total of 3031 intensities were collected on a Philips PW-1100 four-circle diffractometer (M Kα radiation) by using the θ–2θ scan method. The data have been analyzed by using the MULTAN program. The positional and anisotropic thermal parameters of all nonhydrogen atoms were refined by full-matrix least-square calculations. The resulting R factor is R = 0.060 for the 2095 reflections having $I \geq 3\sigma(I)$.

Supplementary Material Available: Final atomic thermal parameters, bond distances, and bond angles (4 pages). Ordering information is given on any current masthead page.

(23) Kadaba, P. K.; Triplett, J. *Heterocycles* **1978** *9*, 243.

Synthesis of (+)-(Neomenthylsulfonyl)methyl Isocyanide. Synthesis and Absolute Configuration of (*R*)-(+)-2-Methylcyclobutanone and (*S*)-(−)-2-Methylcyclobutanone†

Daan van Leusen, Pieter H. F. M. Rouwette, and Albert M. van Leusen*

Department of Organic Chemistry, Groningen University, Nijenborgh 16, Groningen, The Netherlands

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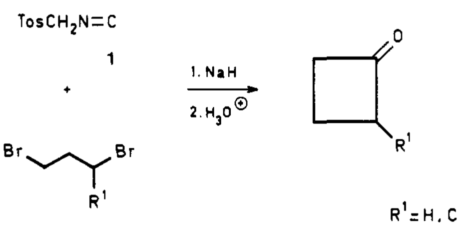
Menthol is used for the synthesis of optically pure (+)-(neomenthylsulfonyl)methyl isocyanide (NeSMIC, 8), which is the first chiral sulfonylmethyl isocyanide reported. This NeSMIC is applied to a two-step synthesis of (*R*)-(+)-2-methylcyclobutanone (12), as well as its enantiomer (11), neither of which have been reported previously. The absolute configurations of 11 and 12 are determined by the octant rule and by an independent chiral synthesis.

Umpolung reactions of sulfonylmethyl isocyanides have found useful synthetic applications.[1] For example, tosylmethyl isocyanide (TosMIC, 1) is a formaldehyde (di)anion equivalent, which has been applied to the synthesis of several carbonyl compounds.[1,2] By this method an extremely simple synthesis of cyclobutanones was developed recently, which for $R^1 = CH_3$ leads to racemic 2-methylcyclobutanone (when racemic 1,3-dibromobutane is used, eq 1).[3]

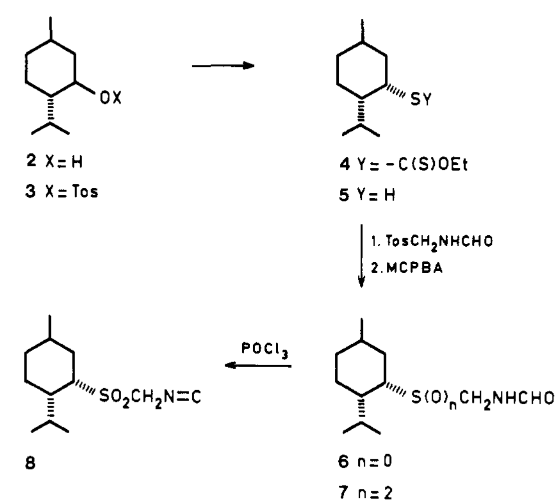


(1)

The purpose of this paper is twofold: (a) to describe the first useful chiral analogue of TosMIC, i.e., (+)-(neomenthylsulfonyl)methyl isocyanide (NeSMIC, 8), and (b) to initiate its application by the first synthesis of optically active 2-methylcyclobutanone, (−) as well as (+) (**11** and **12**, respectively, Scheme II). Moreover, **12** is prepared also from TosMIC and (*S*)-(+)-1,3-dibromobutane (eq 1), and the absolute configuration is determined to be *R*.

Synthesis of (+)-(Neomenthylsulfonyl)methyl Isocyanide (8). Several possibilities may be considered in designing chiral analogues of TosMIC.[4] For synthetically meaningful purposes[5] chirality preferably is introduced in the group R* of $R^*SO_2CH_2N{=}C$ by using optically pure and readily available starting materials.[6,7] The best results so far have been obtained with (−)-menthol.[8] By use of essentially known chemistry, (−)-menthol (**2**) can be converted in six steps in 26% overall yield to (+)-(neo-

Scheme I

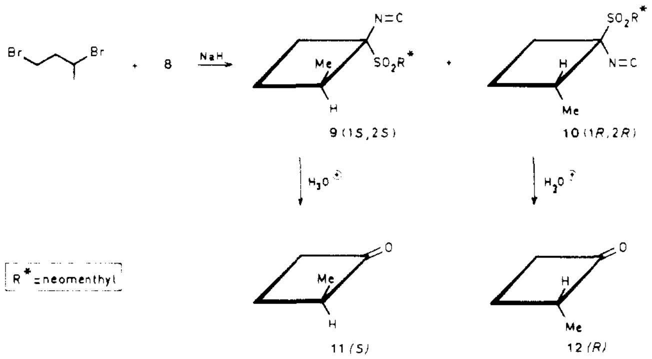


† Chemistry of Sulfonylmethyl Isocyanides 22. For part 21 see ref 2c.

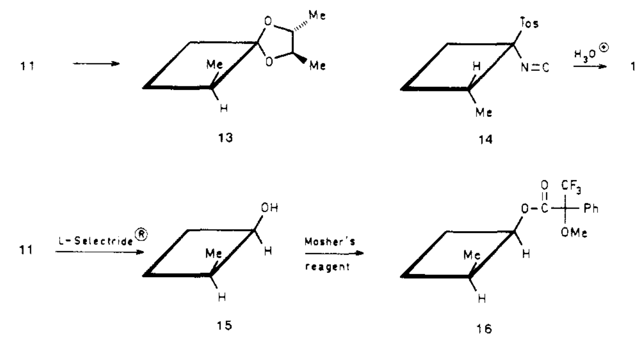
(1) Brief review: van Leusen, A. M. *Lect. Heterocycl. Chem.* **1980**, *5*, S111.
(2) (a) Possel, O.; van Leusen, A. M. *Tetrahedron Lett.* **1977**, 4229. (b) van Leusen, D.; van Leusen, A. M. *Ibid.* **1977**, 4233. (c) van Nispen, S. P. J. M.; Mensink, C.; van Leusen, A. M. *Ibid.* **1980**, 3723.
(3) van Leusen, D.; van Leusen, A. M. *Synthesis* **1980**, 325.
(4) Rouwette, P. H. F. M., Ph.D. Dissertation, Groningen University, 1979.
(5) Work describing synthetic applications based on asymmetric inductions with **8** is in progress.
(6) Chirality in compounds TosCHRN=C (R = alkyl, aryl; such compounds have indeed been prepared but were not resolved) will be lost via the conjugate bases, which are essential in most of their synthetic applications (see ref 1).
(7) Alternatively, partially resolved sulfoximinomethyl isocyanide PhSO(=NTos)$CH_2N{=}C$ (mp 96 °C dec) was prepared and investigated previously: van Leusen, D., unpublished results, 1975–1977.

0022-3263/81/1946-5159$01.25/0

Scheme II



Scheme III



menthylsulfonyl)methyl isocyanide (**8**, Scheme I), which is a stable crystalline compound melting at 68 °C.

The preparation of (+)-neomenthane-3-thiol (**5**) from (–)-menthol has been described previously.[9] We were able to improve the overall yield from 14% to 40% by using DMF, instead of acetone, as the solvent in the reaction step **3** → **4** (i.e., nucleophilic displacement of TosO by EtOC(S)S). For the conversion of **5** to **6** the use of strong base (*t*-BuOK or NaH) was necessary to displace the tosyl group of *N*-(tosylmethyl)formamide by neomenthanethiolate (95% yield), as compared with Et_3N applied previously in similar reactions of aromatic thiols.[10] After oxidizing sulfide **6** (with MCPBA in 95% yield), dehydration of formamide **7** in the usual way ($POCl_3$, Et_3N) gave (+)-(neomenthylsulfonyl)methyl isocyanide (**8**) in 73% yield (26% based on **2**).

NeSMIC (**8**) obviously is an epimerically pure (^{13}C NMR, sharp melting point) and, therefore, an optically pure compound ($[\alpha]_D$ +42.7°, $[\alpha]_{578}$ +46.2°; $CHCl_3$). Essential to the configuration of NeSMIC is the reaction **3** → **4**, which according to Beretta et al. takes place with at least 95% inversion.[9,11] The ^1H NMR of **8** shows a well-resolved AB quartet for the diastereotopic $C(\alpha)H_2$ group around δ 4.48 (J = 15 Hz) and a broad peak for C(2)H at δ 3.80 with W_H = 8 Hz, indicative of an equatorial position of this hydrogen.[12]

Synthesis of Optically Active 2-Methylcyclobutanones (11 and 12). Absolute Configuration. Reaction of NeSMIC (**8**) with racemic 1,3-dibromobutane leads to a 1:1 mixture of only two diastereomeric cyclobutane derivatives, to which we assign structures **9** and **10**. The assignment of absolute configurations, as in Scheme II, will be discussed below.

Hydrolysis of the mixture of **9** and **10** with H_2SO_4 and a calculated amount of water in sulfolane, as described previously for the corresponding tosyl analogues, gave 73% of pure but racemic 2-methylcyclobutanone. Separation of the diastereomers **9** and **10** was achieved by analytical HPLC, and, for preparative purposes, by fractional crystallization from pentane. Thus, from 4.86 g of **8** was obtained 1.6 g (27%) of pure **9** (mp 66–67 °C; $[\alpha]_{578}$ +79.2°) by three crystallizations and 300 mg (5%) of pure **10** (mp 48–50 °C; $[\alpha]_{578}$ +17.2°) by six crystallizations. Both **9** and **10** were at least 95% pure by ^1H NMR.

Hydrolysis of **9** and **10**, separately, leads to the enantiomeric, optically active 2-methylcyclobutanones **11** and **12**, respectively. In these reactions the chemical yield and enantiomeric excess (ee) of the products are inversely related, depending on the reaction conditions. Thus, optically pure **9** gave (*S*)-2-methylcyclobutanone (**11**) in 87% yield with an ee of 43% when the reaction was carried out for 2 h at a temperature up to 80 °C, whereas reaction for 0.5 h at 50 °C gave 44% of **11** with an ee of 62% ($[\alpha]_{578}$ –12.3°). Likewise, **10** gave 60% of (*R*)-2-methylcyclobutanone (**12**), $[\alpha]_{578}$ +11.0°. A chloroform solution of **12** was optically stable for at least 2 months, but racemization was observed upon addition of HCl. This is consistent with loss of the enantiomeric excess during the formation of **11** and **12** (from optically pure **9** and **10**, respectively) by partial racemization of the product during the acid-catalyzed hydrolysis. The ee of **11** was determined by two different methods: (a) using the ^{13}C NMR method of Hiemstra and Wynberg[13] on 1,3-dioxolane **13** (Scheme III) derived from **11** and (*R,R*)-(–)-butane-2,3-diol; (b) by ^{19}F NMR on the Mosher derivative[14] **16** of *cis*-2-methylcyclobutanol (**15**) obtained by stereoselective reduction of **11** with lithium tri-*sec*-butyl borohydride.[15] On the assumption of a linear dependence of the ee on rotation and no decrease in the ee during derivatizations, the rotation of optically pure **11** in $CHCl_3$ is calculated to be $[\alpha]_{578}$ –20.9° and –19.8° for methods a and b, respectively.

The absolute configurations of **11** and **12** were established by two independent methods. First of all this was done by preparing (+)-2-methylcyclobutanone (i.e., **12**) from TosMIC and partially resolved (*S*)-(+)-1,3-dibromobutane[16] according to eq 1 (also Scheme III, **14**). In the ring-closing step to give **14**, displacement of the 3-bromine, with inversion (see Discussion and ref 16), leads eventually to (+)-2-methylcyclobutanone (**12**), which therefore has the *R* configuration. This compound, further, shows a negative Cotton effect in ORD and CD ($\Delta\epsilon$ = –0.2, λ 306 nm, ee 64%; Figure 1), which by application of the octant rule once again establishes the *R* configuration of **12**.

Discussion

No optical properties of 2-methylcyclobutanone have been reported so far, even though the compound was

(8) Another obvious starting material, (+)-10-camphorsulfonic acid, was converted in four steps into the corresponding sulfonylmethyl isocyanide (26% overall yield). However, this isocyanide, obtained as a viscous oil, was not completely stable; also, the camphor keto group was interfering in some of its reactions.[4]

(9) Beretta, E.; Cinquini, M.; Colonna, S.; Fornasier, R. *Synthesis* **1974**, 425.

(10) Olijnsma, T.; Engberts, J. B. F. N.; Strating, *J. Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 209.

(11) Additional support for this view is given in ref 4: $LiAlH_4$ reduction of a cycloadduct of **8** and acetophenone results in formation of neomenthanethiol **5** with the same rotation ($[\alpha]_D$ +47°), which further shows the absence of epimerization at C2 in all reactions involved.

(12) Jackmann, L. M.; Sternhell, S. "Applications of NMR-Spectroscopie in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; p 288.

(13) (a) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183. (b) Hiemstra, H. Ph.D. Dissertation, Groningen University, 1980.

(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(15) Brown, H. C.; Krishmamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(16) Paquette, L. A.; Freeman, J. P. *J. Org. Chem.* **1970**, *35*, 2249.

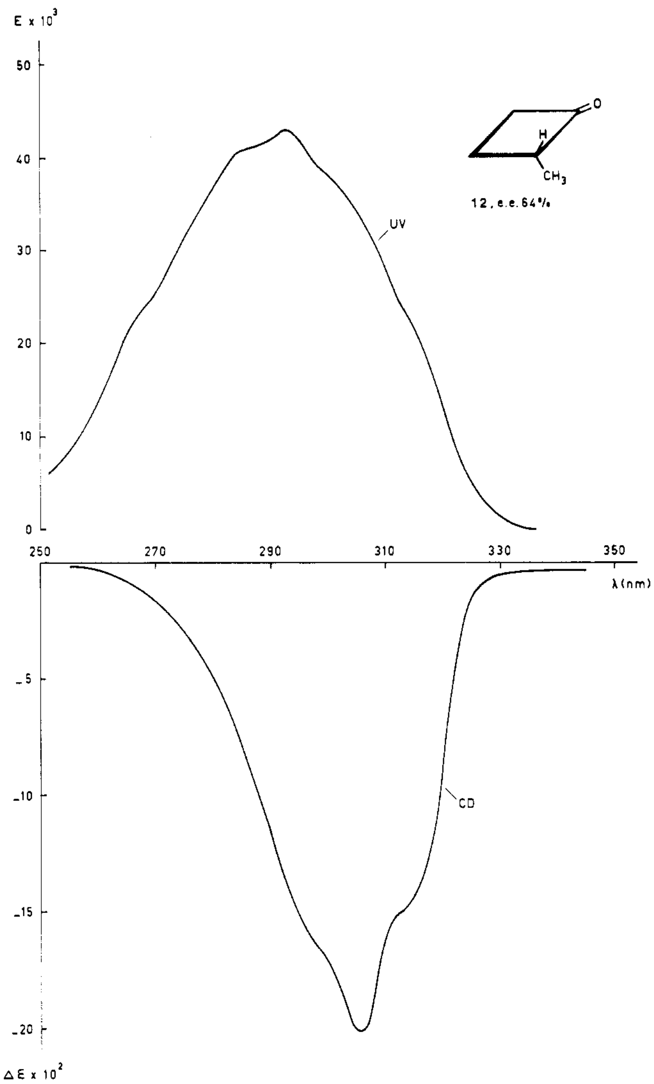
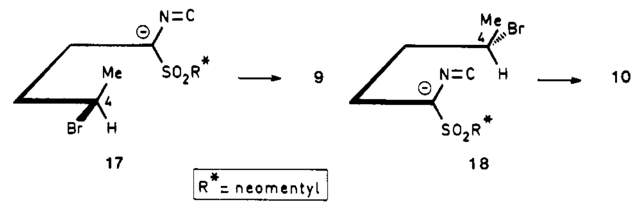


Figure 1. UV and CD spectra of (*R*)-2-methylcyclobutanone (**12**, ee 64%) in isooctane.

identified recently as a component of the lipid extract of *Hevea basiliensis*.[17] Apparently our paper is the first to describe optically active 2-methylcyclobutanones (**11** and **12**). The octant rule has been shown by Conia and Gore to apply to cyclobutanones for a number of tri- and tetrasubstituted derivatives[18] and has since been used occasionally to determine the configuration of some more complex cyclobutanones.[19] A solution of (+)-2-methylcyclobutanone in isooctane shows a negative Cotton effect in CD (Figure 1) and ORD for material with 64% ee. According to the octant rule this material (**12**) therefore has the *R* configuration (which, as a matter of fact, is true for both conformers, with the CH_3 in either a pseudoequatorial or pseudoaxial position). The preparation of (+)-**14** from (*S*)-1,3-dibromobutane and TosMIC is fully consistent with this assignment and, moreover, proves the inversion in the ring closure to **14**.

Through the above assignment the absolute configuration of C(2) of all chiral compounds in Schemes II and III is established as indicated. The assignments of the C(1)

Scheme IV



configuration of **9** and **10** (and **14**) are based on the following. Reaction of NeSMIC (**8**) with (±)-1,3-dibromobutane gives *two* diastereomers only, which therefore can only be **9** and **10** or the corresponding pair of cis epimers.[20] The most reasonable sequence of reactions leading to **9** and **10** involves displacement of the primary bromine by the anion of NeSMIC, followed by an S_N2-type ring closure (as with **14**) of the anions **17** and **18** depicted in Scheme IV. The energetically most favorable path of the last step will require the largest substituents (Me and Tos) to be in a trans position as indicated.[21] Each of the two configurations at C(4) in **17** and **18** will then need a different diastereotropic face of the (assumedly) flat carbanion to react. When steric factors are significant, such a process would lead to a mixture of **9** and **10** only, otherwise a mixture of *four* diastereomers could be envisioned (i.e., **9** and **10** plus two cis epimers) but not of the cis epimers only. Epimerization of the cis epimers to **9** and **10** after ring closure is hard to explain.

Experimental Section

General Methods. ^1H NMR spectra were recorded on a 60-MHz Hitachi Perkin-Elmer R-24B or a 100-MHz Varian XL-100 (FT) apparatus in δ units downfield from internal Me_4Si. The latter instrument was used also for ^{13}C and ^{19}F work. For reported multiplicity of ^{13}C NMR signals only $^1J_{C-H}$ values were considered. Optical activity was measured on a Perkin-Elmer 241 polarimeter using 10-cm cells. Circular dichroism was measured on a Cary 60 instrument in a 1-cm cell. Both measurements were carried out at room temperature (20–22 °C). HPLC was carried out on a Waters LC Model 6000A apparatus. The following instruments have been used: AEI 902 (mass spectra), Unicam SP-200 (IR), Zeiss PMQII (UV), Varian 1400 (GLC). The elemental microanalyses were carried out in the Analytical Department of our laboratory.

(+)-Neomenthane-3-thiol (5). The procedure of Beretta et al.[9] was improved. In an efficiently operating hood, a stirred suspension of (−)-menthyl *p*-toluenesulfonate[9] (**3**; 100 g, 0.32 mol) and potassium ethylxanthate (86 g, 0.42 mol) in dimethylformamide (DMF, 400 mL) was heated at 60–70 °C for 48 h. The cooled mixture was poured in ice–water (2 L) and extracted with $CHCl_3$ (4 × 150 mL). The combined extracts were washed twice with aqueous NaCl (5%, 200 mL), dried ($MgSO_4$), and concentrated. The crude xanthate (still containing some DMF) was stirred with 1,2-diaminoethane (150 mL) for 15 h at room temperature under nitrogen, according to the procedure of Mori et al.[22] After the workup the crude thiol was distilled to give 24.3 g (45%) of **5**: bp 91–94 °C (11–12 mmHg); $[\alpha]_D$ +47.8° (*c* 2.06, $CHCl_3$) [lit.[9] $[\alpha]^{25}_D$ +39.0° ($CHCl_3$)]. Rotations are probably affected by traces of (−)-menthol.

(+)-*N*-[(Neomenthylthio)methyl]formamide (6). To an ice-cooled, stirred solution of (+)-neomenthane-3-thiol (**5**; 22.0

(17) Nishimura, H.; Philp, R. P.; Calvin, M. *Phytochemistry* **1977**, *16*, 1048.

(18) Conia, J. M.; Gore, J. *Bull. Soc. Chim. Fr.* **1964**, 1968. Gore, J.; Djerassi, C.; Conia, J. M. *Ibid.* **1967**, 950.

(19) See for example: Bates, R. B.; Onore, M. J.; Paknikar, S. K.; Steelink, C. *Chem. Commun.* **1967**, 1037. Subramanian, L. R.; Rao, G. S. K. *Can. J. Chem.* **1969**, *47*, 1147. Bertrand, M.; Gras, J. L.; Gore, J. *Tetrahedron Lett.* **1972**, 1189.

(20) Any other pair of four conceivable combinations of, for example, *trans*-**9** with only one cis epimer of **10** is most unlikely and cannot reasonably be accounted for by energy arguments.

(21) Previous experiences with cyclic (*trans*-5-methyl-5-*tert*-butyl-4-tosyl-2-oxazoline) as well as acyclic compounds [(*E*)-1-isocyano-1-tosylalkenes] show an exclusive preference for trans-positioned tosyl and alkyl groups: Oldenziel, O. H., Ph.D. Dissertation, Groningen University, 1975. van Leusen, A. M.; Schaart, F. J.; van Leusen, D. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 258.

(22) Mori, K.; Nakamura, Y. *J. Org. Chem.* **1969**, *34*, 4170.

g, 0.13 mol) in a mixture of ether (100 mL) and Me_2SO (50 mL) was added in 0.5 h 16.0 g (0.14 mol) of solid *t*-BuOK. After the mixture was stirred for 1 h at room temperature, solid *N*-(tosylmethyl)formamide[23] (27.7 g, 0.13 mol) was added in portions in 0.5 h under cooling with ice–water. The mixture was stirred for 5 h at room temperature, poured in ice–water (300 mL), and extracted with ether (3 × 100 mL). The combined extracts were washed with water and with brine, dried ($MgSO_4$), and concentrated to give 28 g (95%) of **6** as a viscous oil, which was at least 95% pure by NMR: ^1H NMR ($CDCl_3$) δ 0.5–2.3 (m, 18), 3.3 (br, 1), 4.0–4.8 (m, 2), 7.4 (br, 1), 8.22 (d, 1); mass spectrum, *m/e* 229.151 (M^+; calcd 229.150); $[\alpha]_D$ +80.7° (*c* 2.24, $CHCl_3$).

(−)-*N*-[(Neomenthylsulfonyl)methyl]formamide (7). To an ice-cooled, stirred solution of sulfide **6** (23.0 g, 0.10 mol) in CH_2Cl_2 (250 mL) was added in 0.5 h 40 g (0.20 mol) of *m*-chloroperbenzoic acid (MCPBA, technical grade, 85%). The mixture was stirred for 5 h at room temperature and filtered. The filter cake was extracted with CH_2Cl_2 (100 mL), and the combined filtrate and extract were washed with aqueous $NaHCO_3$ (10%, 200 mL) and with water (200 mL), dried ($MgSO_4$), and concentrated. The resulting oil was crystallized from 1:20 EtOH–petroleum ether (bp 60–80 °C) to give 24.8 (95%) of **7**, mp 85–88 °C. Analytically pure material was obtained from the same solvent mixture: mp 86.4–87.8 °C; IR (Nujol) 3390 (NH), 1680 and 1540 (NHCHO), 1280 and 1120 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.7–2.6 (m, 18), 3.57 (br, 1), 4.29 and 4.79 (d of AB q, *J* = 7, 15 Hz, 2), 7.80 (br t, *J* = 7 Hz, 1), 8.30 (s, 1); $[\alpha]_D$ −20.5° (*c* 1.95, $CHCl_3$). Anal. Calcd for $C_{12}H_{23}NO_3S$: C, 55.14; H, 8.87; N, 5.36; S, 12.27. Found: C, 55.25; H, 8.88; N, 5.36; S, 12.24.

(+)-(Neomenthylsulfonyl)methyl Isocyanide (8). The (sulfonylmethyl)formamide **7** (20.9 g, 80 mmol) was dehydrated with $POCl_3$ and Et_3N by following the procedure [23b] used for the synthesis of TosMIC. The workup was as follows. After the addition of $POCl_3$ was complete, the mixture was stirred for 0.5 h at 0 °C and then poured in ice–water. Extraction with $CHCl_3$ gave crude **8** (15.6 g, 80%), which was chromatographed rapidly with CH_2Cl_2 over neutral alumina and then crystallized from EtOH–petroleum ether (bp 60–80 °C) to give colorless crystals: 14.1 g (73%); mp 65.0–67.5 °C. Analytically pure material was obtained from the same solvent mixture: mp 67.7–68.4 °C; IR (Nujol) 2180 (N≡C), 1330 and 1130 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.7–2.5 (m, 18), 3.80 (br, W_H = 8 Hz), 4.27 and 4.58 (AB q, *J* = 15 Hz, 2); ^{13}C NMR ($CDCl_3$) δ 21.4, 21.6, and 21.9 (3 q, $J \approx 125$ Hz, 3 CH_3), 24.6 (t, $J \approx 125$ Hz, C(6)), 26.3 (d, *J* = 125 Hz, $CH(CH_3)_2$), 29.3 (d, *J* = 125 Hz, C(4)), 34.6 and 36.1 (2 t, *J* = 125 Hz, C(3) and C(5)), 48.9 (d, *J* = 125 Hz, C(1)), 58.8 (d, *J* = 140 Hz, C(2)), 59.8 (t, *J* = 155 Hz, C(α)), 165.8 (s, N≡C); $[\alpha]_D$ +42.7° (*c* 1.60, $CHCl_3$), $[\alpha]_{578}$ +46.2° (*c* 1.68, $CHCl_3$). Anal. Calcd for $C_{12}H_{21}NO_2S$: C, 59.22; H, 8.70; N, 5.76; S, 13.17. Found: C, 59.26; H, 8.77; N, 5.78; S, 13.13.

1-Isocyano-*t*-2-methyl-*r*-1-(neomenthylsulfonyl)cyclobutane (9 + 10). Hydrolysis and Separation of Diastereomers. A solution of (+)-(neomenthylsulfonyl)methyl isocyanide (**8**; 2.43 g, 10.0 mmol) together with racemic 1,3-dibromobutane (2.20 g, 10.2 mmol) in a mixture of Me_2SO (5 mL) and Et_2O (2.5 mL) was added dropwise in 20 min to a suspension of NaH (1.2 g, 24 mmol; 50% dispersion in mineral oil, which was removed previously with pentane) in Me_2SO (20 mL) and Et_2O (10 mL) at room temperature under N_2. After the mixture was stirred for 1.5 h, water (10 mL) was added slowly, and the mixture was extracted with Et_2O (4 × 25 mL). The combined extracts were washed with saturated aqueous NaCl (3×), dried (Na_2SO_4), and concentrated. The resulting brown oil was dissolved in Et_2O, filtered over a layer of alumina (diameter 3 cm, thickness 2 cm), and concentrated once again to give 2.95 g of an oil consisting of a 1:1 mixture of two diastereomers only (**9** and **10**), according to analytical HPLC (see below) and ^1H NMR (the latter being a nice superposition of the spectra of separated **9** and **10**, as discussed below): $[\alpha]_{578}$ +40° (*c* 1.8, $CHCl_3$); IR (neat) 2160 (N≡C), 1310, 1330, and 1130 cm^{-1} (SO_2).

The total amount of crude **9** + **10** (2.9 g) was hydrolyzed with H_2SO_4 (0.6 mL) and water (0.2 mL) in sulfolane (tetramethylene sulfone, 10 mL) according to the procedure described for 1-isocyano-2-methyl-1-tosylcyclobutane,[3] at a temperature which was raised gradually to 80 °C in the course of 2 h, to give 0.610 g (73% based on **8**) of pure (±)-2-methylcyclobutanone ($[\alpha]_{578}$ +0.05° (*c* 2.0, $CHCl_3$)) with the same spectral and physical data as reported previously.[3]

Analytical HPLC (silica gel; with CH_2Cl_2–hexane, 26:74, isocratically at 20 °C) followed by crystallization from petroleum ether (bp 40–60 °C) was used to obtain pure samples of **9** and **10** separately. For preparative purposes only fractional crystallization from pentane was used. On a 20-mmol scale (4.86 g of **8**, as above), 1.60 g (27%) of pure **9** (1*S*,2*S* configuration, see below) was obtained after three crystallizations: mp 66–67 °C; $[\alpha]_{578}$ +79.2° (*c* 1.02, $CHCl_3$); ^1H NMR δ 0.8–4.1 (m), which on enlargement showed seven of the expected eight CH_3 peaks well separated at δ 0.84, 0.90, 0.96, 1.00 (two peaks coinciding), 1.11, 1.23, and 1.36. The other diastereomer (**10**, 1*R*,2*R* configuration; see below) was obtained pure after six crystallizations with the help of seeding crystals obtained via the HPLC separation: yield 300 mg (5%); mp 48–50 °C; $[\alpha]_{578}$ +17.2° (*c* 0.57, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.7–4.2 (m), which on enlargement showed eight CH_3 peaks, four separately and four as split peaks at δ 0.80, 0.88 and 0.91, 1.00 and 1.03, 1.13, 1.20, and 1.32. Anal. Calcd for $C_{16}H_{27}NO_2S$: C, 64.61; H, 9.15; N, 4.71; S, 10.78. Found: C, 64.75; H, 9.11; N, 4.72; S 10.85.

(*S*)-2-Methylcyclobutanone (11). Hydrolysis (2 h, 80 °C) of pure (1*S*,2*S*)-isocyanide **9** (1.485 g, 5 mmol) as described above for the mixture of **9** and **10**, with H_2SO_4 (0.3 mL), water (0.2 mL), and sulfolane (5 mL), gave 367 mg (87%) of **11**: $[\alpha]_{578}$ −9.0° (*c* 1.07, $CHCl_3$); ee 43% (see below); the GLC (SE-30, 75 °C) was identical with that of compound **12** (below), both showing a small impurity peak, ratio 1:21 (retention time × peak height). Reduction of the time and temperature of hydrolysis to 0.5 h and 50 °C lowered the chemical yield to 185 mg (44%) of **11** but improved the optical purity to $[\alpha]_{578}$ −12.3° (*c* 0.38, $CHCl_3$) [ee 62% (see below); pure by GLC (same conditions as above)]. After the remainder of the reaction mixture was heated for another 1 h at 50–100 °C, without vacuum, a second crop (155 mg, 37%) of *racemized* 2-methylcyclobutanone was obtained.

(*R*)-2-Methylcyclobutanone (12). From 10. Analogously to the synthesis of **11** (reaction time 1 h), pure (1*R*,2*R*)-isocyanide **10** (297 mg, 1 mmol) was hydrolyzed with H_2SO_4 (0.06 mL) and water (0.04 mL) in sulfolane (2 mL) to give 50 mg (60%) of **12**, $[\alpha]_{578}$ +11.0° (*c* 0.86, $CHCl_3$). GLC-pure material (same conditions as with **11**) was obtained in lower yield (24%) in 5 min at 50 °C: $[\alpha]_{578}$ +12.7° (*c* 0.31, $CHCl_3$), ee 64% (calcd from **11**); UV (48.78 mg in 25 mL of isooctane) λ_{max} 293 nm (ϵ_{max} 22.1); CD (8.5 mg in 10 mL of isooctane) Δ_ϵ −0.2, λ 306 nm.

From 14. According to the procedure of ref 3 (1*R*,2*R*)-(−)-1-isocyano-2-methyl-1-tosylcyclobutane (**14**; see below; 380 mg, 1.55 mmol; $[\alpha]_{578}$ +1.4°) was hydrolyzed to give 60 mg (47%) of **12**, $[\alpha]_{578}$ +0.89° (*c* 1.0, $CHCl_3$).

(1*R*,2*R*)-(−)-1-Isocyano-2-methyl-1-tosylcyclobutane (14) was prepared according to ref 3 from crude (*S*)-(+)-1,3-dibromobutane[16] (from 1.33 g, 5.4 mmol, of (*S*)-1,3-butanol dimethanesulfonate and LiBr) and TosMIC[23] (7.88 mg, 4.0 mmol) in a yield of 400 mg (40%) ($[\alpha]_{578}$ −1.4° (*c* 0.42, $CHCl_3$)) together with a second crop obtained from the mother liquor of 180 mg (18%); $[\alpha]_{578}$ −3.0° (*c* 0.66, $CHCl_3$). The compound was spectroscopically identical with racemic material obtained previously.[3]

(2*R*,3*R*,6*S*)-2,3,6-Trimethyl-1,4-dioxaspiro[3.4]octane (13). Determination of the Enantiomeric Excess by ^{13}C NMR. According to the method that Hiemstra and Wynberg[13] used for cyclohexanones, (*S*)-2-methylcyclobutanone (**11**; 250 mg, 3.0 mmol; $[\alpha]_{578}$ −9.0°) and (*R*,*R*)-(−)-butane-2,3-diol (270 mg, 3.0 mmol) were refluxed in benzene (2.5 mL) for 1.5 h with one crystal of *p*-toluenesulfonic acid monohydrate and some $MgSO_4$. The mixture was concentrated, dissolved in ether, and filtered over a layer (2 cm thick) of alumina (activity II–III), concentrated, and distilled in a short-path apparatus to give 390 mg (83%) of acetal: bath temperature 30–70 °C (13 mmHg); ^1H NMR ($CDCl_3$, 100 MHz) methyl peaks at δ 0.97 and 1.09 show a diastereomerical splitting in a ratio of ca. 1:2; ^{13}C NMR ($CDCl_3$, only of major diastereomer) δ 12.8 (q, C(6)CH_3), 16.4 (q, C(2)CH_3, C(3)CH_3), 19.4 (t, C(7)), 34.3 (t, C(8)), 42.7 (d, C(6)), 77.4 and 78.2 (2 d, C(2), C(3)), 109.2 (s, C(5)); next to the signals of C(7), C(6), and C(5) smaller peaks

(23) (a) Purchased from Ofichem, Gieten, Holland. (b) Procedure: Hoogenboom, B. E.; Oldenziel, O. H.; van Leusen, A. M. *Org. Synth.* **1977**, *57*, 102.

are found at $\Delta\delta$ values of only 0.20–0.25 ppm; that for (C6)CH_3, however, was at $\Delta\delta$ = 1.20 ppm. From the latter peaks (at δ 12.8 and 14.0) the ratio of diastereomers (14 and its 6*R* epimer) was determined accurately[13b] to be 1:2.5; i.e., the ee is 43%.

(1*R*,2*S*)-2-Methylcyclobutanol (15). A solution of (*S*)-2-methylcyclobutanone (11; $[\alpha]_{578}$ −12.3°; 168 mg, 2.0 mmol) in THF (1 mL) was added to 2.8 mL of a solution of lithium tri-*sec*-butylborohydride[15] (L-Selectride, Aldrich; 1 M in THF, 2.8 mmol) at −80 °C under N_2. After the mixture was stirred for 2 h at −80 °C, the temperature was raised to room temperature (1 h). To the mixture were added water (0.4 mL), EtOH (1.5 mL), 6 M NaOH (1 mL), and, carefully, 30% H_2O_2 (1.5 mL), and stirring was continued for 2 h at room temperature. The organic layer was separated, the water layer was extracted twice with ether, the combined organic layers were washed with brine and dried (Na_2SO_4), and the ether was removed through a Vigreux column. The residue was purified twice by GLC (12-ft LAC-3-R-728 column, 80 °C) to give the cis alcohol 15: $[\alpha]_{578}$ +13.7° (*c* 0.39, $CHCl_3$); IR (neat) 3450 cm^{-1} (OH); ^{1}H NMR (CCl_4) δ 1.05 (d, *J* = 8 Hz, 3), 2.00 (s, 1), 1.2–2.7 (m, 6), 4.29 (q, *J* = 8 Hz, 1).

The cis alcohol 15 was reacted with 1 equiv of the acid chloride of optically pure α-methoxy-α-(trifluoromethyl)benzeneacetic acid (Aldrich), according to Mosher et al.[14] in pyridine overnight at room temperature, followed by extraction with ether, washing with aqueous $NaHCO_3$, and drying, to give the acetate 16 as an oil; ^{1}H NMR (CCl_4) δ 0.98 and 1.07 (2 d, *J* = 7 Hz, 3, ratio ca. 1:4), 1.0–3.0 (m, 5), 3.48 (d, *J* = 1 Hz, 3), 5.15 (br q, *J* = 7 Hz, 1), 7.3 (br, 5); ^{19}F NMR (C_6D_6–CCl_4, 1:1) δ −76.54 and −76.69 in a ratio of 36:152, i.e., 62% ee.

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Registry No. 1, 36635-61-7; **2**, 2216-51-5; **3**, 2230-82-2; **4**, 79357-06-5; **5**, 53273-24-8; **6**, 79357-07-6; **7**, 79357-08-7; **8**, 79357-09-8; **9**, 79357-10-1; **10**, 79390-62-8; **11**, 79390-63-9; **12**, 79390-64-0; **13** (6*S* epimer), 79357-11-2; **13** (6*R* epimer), 79433-79-7; **14**, 79390-65-1; **15**, 79390-66-2; **16**, 79357-12-3; ethyl xanthate, 151-01-9; *N*-(tosylmethyl)formamide, 36635-56-0; (±)-1,3-dibromobutane, 79390-67-3; (±)-2-methylcyclobutanone, 74528-79-3; (*S*)-(+)-1,3-dibromobutane, 79357-13-4; (*R*,*R*)-(−)-butane-2,3-diol, 24347-58-8; (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 20445-33-4.

Hard Acid and Soft Nucleophile Systems. 5.[1] Ring-Opening Reaction of Lactones to ω-Alkylthio or ω-Arylthio Carboxylic Acids with Aluminum Halide and Thiol

Manabu Node, Kiyoharu Nishide, Masahito Ochiai, Kaoru Fuji, and Eiichi Fujita*

Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan

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Lactones were converted into ω-alkylthio carboxylic acids in high yields through ω-carbon–oxygen bond cleavage when they were treated with aluminum halide and alkanethiol. The aluminum halide and arenethiol system has also been found to be useful for the preparation of the synthetically valuable ω-arylthio carboxylic acids from lactones.

Lactones are important synthetic intermediates. The ring opening of lactones through the alkyl–oxygen bond cleavage with sulfur containing nucleophile, e.g., alkanethiol or arenethiol, is an interesting process because it produces synthetically valuable ω-alkyl(or aryl)thio carboxylic acids: for instance, 4-(phenylthio)butanoic acid and 5-(phenylthio)pentanoic acid can be recyclized to 4-(phenylthio)-γ-butyrolactone and 5-(phenylthio)-δ-valerolactone, respectively, and they can easily be transformed into the corresponding enol lactones.[2]

Excellent syntheses which have not involved a lactone opening procedure have not been reported.[3] Smith,[4] Liotta,[5] and their co-workers reported the conversion of lactones into ω-phenylseleno carboxylic acids by using a powerful nucleophile, phenylselenide anion. ω-Olefinic carboxylic acids were then synthesized. Cleavage of the alkyl–oxygen bond of γ-lactones using lithium thiomethoxide[6] or sodium thioethoxide[3d] has been reported. However, benzyl thiolate has been shown to attack the lactone carbonyl group.[7]

Scheme I

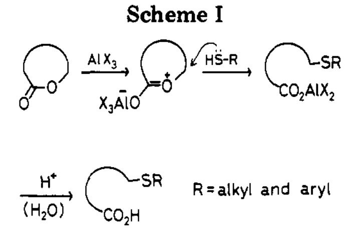
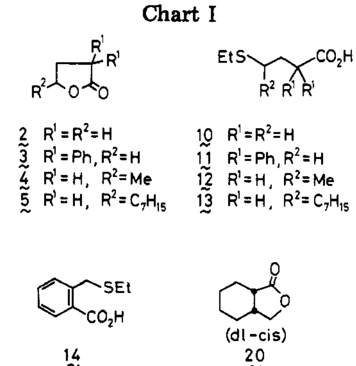


Chart I



(1) For part 4, see: Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662.
(2) Ochiai, M.; Nishide, K.; Node, M.; Fujita, E. *Chem. Lett.* **1981**, 283.
(3) (a) Almond, A. E.; Burditt, A. M.; Douglas, D. E.; Eccles, J. *Can. J. Chem.* **1955**, *33*, 679. (b) Zayed, S. M. A. D.; Mostafa, I. Y.; Farghaly, M. *Arch. Pharm.* (*Weinheim, Ger.*) **1967**, *300*, 526. (c) Cornforth, J. W.; Huang, H. T. *J. Chem. Soc.* **1948**, 1964. (d) Kresze, G.; Schramm, W.; Gleve, G. *Chem. Ber.* **1961**, *94*, 2060.
(4) Scarborough, R. M., Jr.; Smith, A. B., III. *Tetrahedron Lett.* **1977**, 4361.
(5) Liotta, D.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4369.
(6) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859.