Selective Base-Catalyzed Rearrangement of Epoxides into Ketones. Application to γ-Keto Sulfide Synthesis

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A methodology for the selective base-catalyzed isomerization of certain epoxides having a β-proton into ketones is presented. β,γ-Epoxy nitro compounds were the substrates for this transformation and underwent a multistep reaction consisting of epoxide ring opening, isomerization of the double bond, elimination of HNO_2, and addition of PhSH to provide γ-keto sulfides in good yields by reacting with PhSNa or a combination of PhSH and Et_3N. Thus, β,γ-epoxy nitro compounds proved to serve as the synthetic equivalent to α-*exo*-methylene ketones.

Introduction

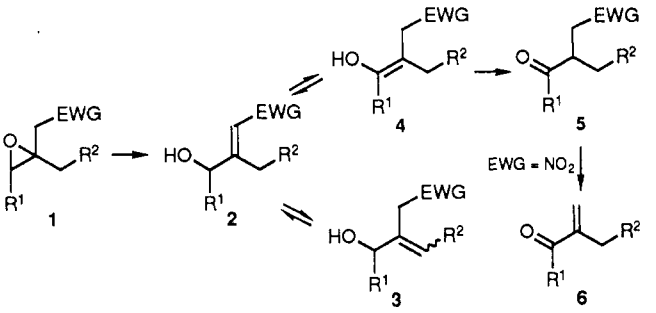
Epoxides have been widely recognized as versatile synthetic intermediates.[3,4] Among their reactions, the base-catalyzed ring opening of epoxides having a β-proton provides a protocol for preparation of allylic alcohols.[4] To the best of our knowledge, however, the base-catalyzed isomerization of the same epoxides to the corresponding ketones is generally a minor reaction pathway.[4] However, the use of protic or Lewis acids has been intensively utilized to rearrange epoxides to carbonyl compounds accompanied by migration of a substituent.[3] Accordingly, the base-catalyzed isomerization of the epoxides to allylic alcohols and the subsequent rhodium-mediated isomerization of the resulting allylic alcohols to ketones constitutes an indirect and general method for this functional group interchange.[5] In addition, the isomerization of certain epoxides to the corresponding ketones has been documented for various transition-metal complexes.[6]

In this paper, we describe a methodology for selective conversion of certain epoxides bearing a β-proton into ketones catalyzed by weak base and an example of its application to organic synthesis. Our approach was based on the base catalyzed equilibration outlined in Scheme I. Trisubstituted epoxides (1) bearing electron-withdrawing group (EWG) on the β-carbon can easily undergo proton abstraction by weak base, followed by the ring opening, to afford allylic alcohols (2). Then, the presence of the EWG must permit 2 to be in equilibrium with allylic alcohols 3 and enols 4 in the presence of a base catalyst. Tautomerization of 4 into 5 should induce the overall shift of the equilibration to 4, eventually leading to the formation of 5.

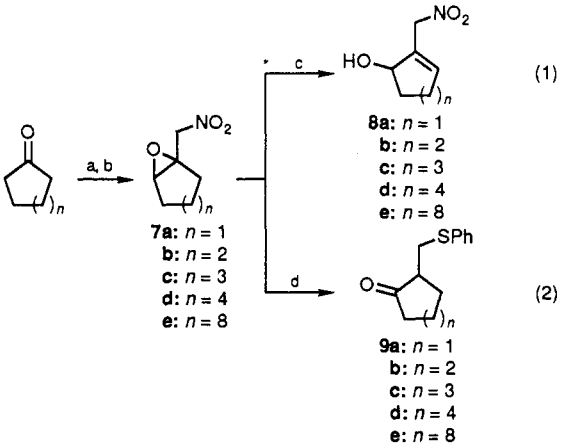
Results and Discussion

To probe our assumption described above, β,γ-epoxy nitro compounds 7, which are readily available from allylic

Scheme I



nitro compounds,[7] were chosen as the substrates because of the high acidity of protons α to the nitro group. Simple treatment of 7 with a catalytic or stoichiometric amount of Et_3N in DMF resulted in the instantaneous disappearance of 7, but failed to give the desired β-nitro ketones (5, EWG = NO_2), or the α-*exo*-methylene ketones (6), but instead produced the allylic alcohols 8[7] or unidentified mixtures,[8] respectively (eq 1). However, the use of stoichiometric amount of PhSNa or a combination of PhSH and Et_3N accomplished the desired reaction to furnish the corresponding γ-keto sulfides (9) (eq 2 and Table I).



(a) CH_3NO_2 (4 equiv), $H_2NCH_2CH_2NMe_2$ (0.3 equiv), PhH, reflux (ref 9); (b) *m*-chloroperbenzoic acid (1 equiv), CH_2Cl_2, 25 °C, 24 h; (c) Et_3N (0.05 equiv), CH_3CN, 25–80 °C (ref 7); (d) PhSNa (2 equiv) or PhSH (2 equiv) and Et_3N (1 equiv), DMF.

In the preparation of seven-membered rings or larger, the use of the PhSH–Et_3N system resulted in a better yield

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(8) Expected product 6 resulting from treatment with 1 equiv of Et_3N may not be tolerant of the reaction conditions.

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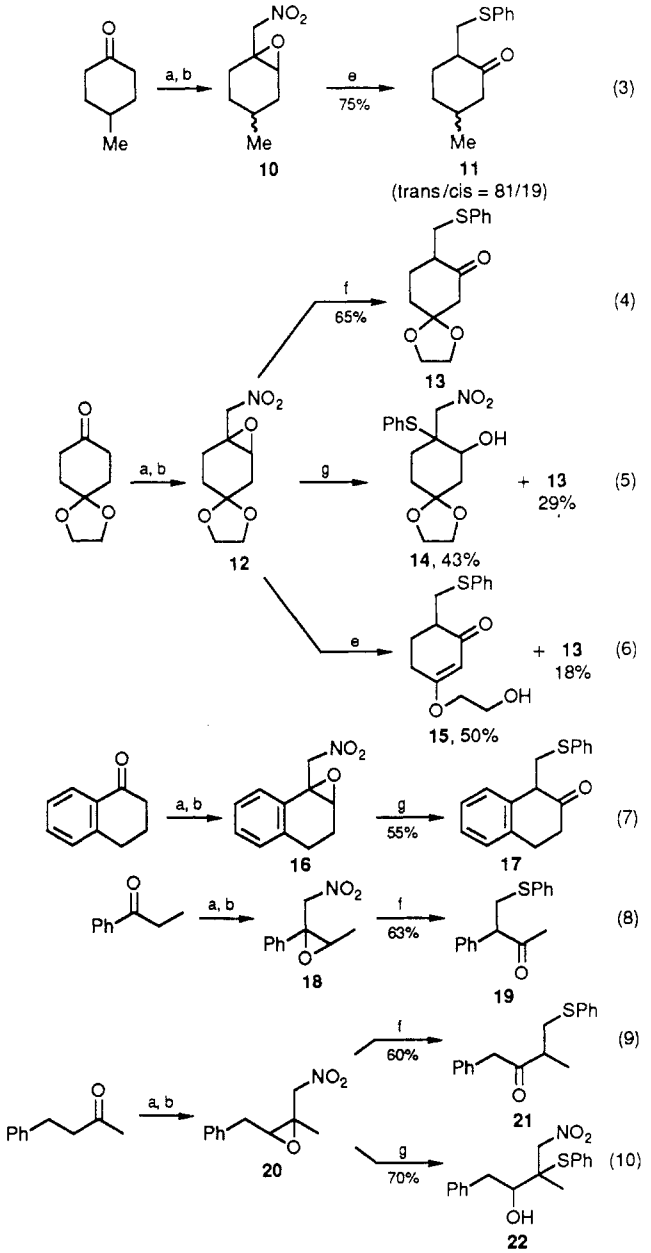
Table I. Selective Conversion of β,γ-Epoxy Nitro Compounds to γ-Keto Sulfides (Eq 2)

run	7	conditions[a]	9, yield (%)[b]
1	**a**, n = 1	A	**a**, 78
2	**b**, n = 2	A	**b**, 85
3	**c**, n = 3	B	**c**, 60 (38)[c] (43)[d]
4	**d**, n = 4	B	**d**, 73 (56)[c] (56)[d]
5	**e**, n = 8	B	**e**, 72 (53)[c]

[a] A: PhSNa (2 equiv), 70 °C, 3 h. B: PhSH (2 equiv) and Et_3N (1 equiv), 25 °C, 24 h. C: PhSNa (2 equiv), 25 °C, 24 h. [b] Isolated yield. [c] Conditions A. [d] Conditions C.

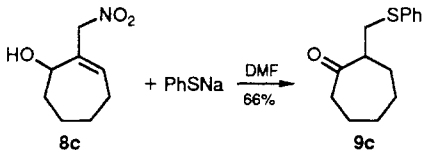
of products (Table I). Such a regioselective approach to γ-keto sulfide synthesis is applicable to various cyclic and acyclic β,γ-epoxy nitro compounds (eq 3–10). As shown in eq 4–6, 9, and 10, careful selection of reaction conditions led to the selective formation of the corresponding γ-keto sulfides; the use of the PhSH–Et_3N system gave the desired products.



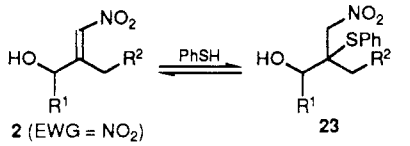
(a) CH_3NO_2 (4 equiv), $H_2NCH_2CH_2NMe_2$ (0.3 or 1.0 equiv), PhH, reflux; (b) MCPBA (1 equiv), CH_2Cl_2, 25 °C, 24 h; (e) PhSNa (2 equiv), DMF, 70 °C, 3 h; (f) PhSH (2 equiv) and Et_3N (1 equiv), DMF, 70 °C, 3 h; (g) PhSH (2 equiv) and Et_3N (1 equiv), DMF, 25 °C, 24 h.

From the standpoint of synthetic utility, *features of the reaction lie in (i) regioselective transposition of original carbonyl oxygen in starting ketones to the neighboring carbon in the products and (ii) introduction of (phenylthio)methyl group into the position of the original carbonyl carbon.* Accordingly, it should be noted that β,γ-epoxy nitro compounds serve as synthetic equivalents to α-*exo*-methylene ketones. The observed regiochemistry of this reaction is defined at the stage of preparation of allylic nitro compounds.[9] Facile regiocontrolled synthesis of allylic nitro compounds from both cyclic and acyclic symmetrical ketones, aryl alkyl ketones, and 2-alkanones[9] ultimately led to the regioselective formation of γ-keto sulfides. In some cases transformations of this type offer an advantage over other methods. For example, γ-keto sulfides **11**, **13**, and **21** are usually not obtainable by the standard synthetic methods such as the Lewis acid catalyzed reaction of keto silyl enol ethers and α-chloromethyl sulfides[10] due to the difficulty in preparing the requisite keto silyl enol ethers regioselectively (eq 3, 4, and 9).[11]

As illustrated in Scheme I, obviously PhS^- or Et_3N itself behaves as a base to induce both the isomerization of **1** (EWG = NO_2) to **4** and the subsequent elimination of HNO_2 from **4** or **5**, and then the concomitantly generated or added PhSH adds to the resulting **6** to form γ-keto sulfides. It is noteworthy that good yields of products are obtained in spite of such a complex multistep reaction. To ascertain the participation of **3** (EWG = NO_2) in the equilibration shown in Scheme I, **8c** was subjected to the same reaction conditions (eq 11). Indeed, γ-keto sulfide



9c was obtained in 66% yield. The formation of γ-hydroxy-β-(phenylthio)-α-nitro compounds **14** and **22** must arise from the Michael addition of PhSH to γ-hydroxy-α-nitro olefins (**2**, EWG = NO_2) (eq 12). Since compounds



14 and **22** were easily converted to the corresponding γ-keto sulfides **13** and **21**, respectively, at the elevated temperature (70 °C) under the same reaction conditions (see eq 4, 5, 9, and 10), it is obvious that **2**, **3**, **4** (EWG = NO_2) and **23** constitute equilibrating mixtures. These results, and the fact that dipolar aprotic solvents such as DMF and DMSO are the suitable reaction medium suggest the proposed mechanism (Scheme I).[12]

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Conclusion

Methodology is presented for the selective base-catalyzed isomerization of certain epoxides to ketones (Scheme I). β,γ-Epoxy nitro compounds (1, EWG = NO_2) undergo a multistep reaction consisting of epoxide ring opening, isomerization of double bond, elimination of HNO_2, and addition of PhSH to produce γ-keto sulfides in good yields by reacting with PhSNa or a combination of PhSH and Et_3N. Thus, β,γ-epoxy nitro compounds serve as synthetic equivalent to α-*exo*-methylene ketones. Overall, the above-mentioned approach serves to yield selectively the allylic alcohol (3) as the kinetic product or ketone (5) as the thermodynamically controlled product using the same epoxide. Thus, this reaction may be applicable to a wide variety of epoxides (1) with other electron-withdrawing groups but NO_2,[13] which can be readily available from the corresponding allylic compounds.

Experimental Section

Infrared spectra were recorded on a JASCO IR-810 spectrophotometer. NMR spectra were measured with either a JEOL FX-90Q or a JEOL GSX-270 instrument in chloroform-*d* using Me_4Si as the internal standard. GLC analyses were performed on a Shimadzu GC-6AM chromatograph using a column packed with Silicon SE30 (3 mm × 2 m). Column chromatography was carried out with Merck silica gel 60 (less than 230 mesh) under moderate pressure (3 atm). Elemental analyses were performed by the Ehime University Advanced Instrumentation Center for Chemical Analysis. All reactions were run under argon. DMF was distilled from CaH_2. Allylic nitro compounds were prepared from the corresponding ketones and nitromethane.[9a]

General Procedure for Epoxidation of Allylic Nitro Compounds. To the allylic nitro compound (30 mmol) in dichloromethane (20 mL) was added *m*-chloroperbenzoic acid (MCPBA) (31 mmol) in dichloromethane (100 mL) at 25 °C. The mixture was stirred at 25 °C for 24 h, and the precipitated *m*-chlorobenzoic acid was removed by filtration. The organic layer was successively washed with 10% sodium bisulfite solution (30 mL), 5% sodium bicarbonate (4 × 30 mL), and saturated sodium chloride solution (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product could be purified by distillation or column chromatography (4:1 hexane–ethyl acetate).

1-(Nitromethyl)cyclopentene oxide (7a):[7b] yield 87%; bp 124–126 °C (14.5 Torr); IR (neat) 1550, 1381, 1237 cm^{-1}; ^1H NMR δ 4.76 (d, *J* = 13.4 Hz, 1 H), 4.60 (d, *J* = 13.4 Hz, 1 H), 3.51 (br s, 1 H), 2.32–1.40 (m, 6 H); ^{13}C NMR δ 77.9, 62.8, 62.5, 28.4, 27.1, 19.5. Anal. ($C_6H_9NO_3$) C, H, N.

1-(Nitromethyl)cyclohexene oxide (7b):[7b] yield 94%; bp 48–50 °C (0.2 Torr); IR (neat) 1552, 1385, 1228 cm^{-1}; ^1H NMR δ 4.52 (d, *J* = 12.9 Hz, 1 H), 4.31 (d, *J* = 12.9 Hz, 1 H), 3.21 (br, 1 H), 2.29–1.71 (br m, 4 H), 1.66–1.00 (br m, 4 H); ^{13}C NMR δ 82.3, 58.0, 56.1, 26.4, 24.3, 19.8, 18.8. Anal. ($C_7H_{11}NO_3$) C, H, N.

1-(Nitromethyl)cycloheptene oxide (7c):[7b] yield 91%; bp 73–75 °C (0.17 Torr); IR (neat) 1540, 1378, 1203 cm^{-1}; ^1H NMR δ 4.44 (s, 2 H), 3.15 (t, *J* = 4.6 Hz, 1 H), 2.22–1.98 (m, 4 H), 1.76–1.04 (br, 6 H); ^{13}C NMR δ 83.0, 61.7, 59.7, 30.8, 30.7, 28.4, 24.2, 24.0. Anal. ($C_8H_{13}NO_3$) C, H, N.

1-(Nitromethyl)cyclooctene oxide (7d): yield 88%; bp 110–112 °C (0.12 Torr); IR (neat) 1550, 1381, 1212 cm^{-1}; ^1H NMR δ 4.88 (d, *J* = 12.3 Hz, 1 H), 4.20 (d, *J* = 12.3 Hz, 1 H), 2.98–2.74 (m, 1 H), 2.44–2.08 (m, 2 H), 1.86–1.22 (m, 10 H); ^{13}C NMR δ 80.1, 61.0, 58.8, 27.4, 26.6, 26.2, 25.5, 25.1. Anal. ($C_9H_{15}NO_3$) C, H, N.

(*E*)- and (*Z*)-1-(nitromethyl)cyclododecene oxide (7e): yield 81%; *E*/*Z* = 82/18; IR ($CHCl_3$) 1552, 1382, 1252, 1233 cm^{-1}; ^1H NMR δ 4.73 (d, *J* = 12.8 Hz, 1 H), and 4.29 (d, *J* = 12.8 Hz, 1 H) [4.94 (d, *J* = 12.8 Hz, 1 H) and 4.27 (d, *J* = 12.8 Hz, 1 H) for *Z*], 2.93 (m, 1 H) [3.13 (dd, *J* = 3.4, 10.4 Hz, 1 H) for *Z*], 2.06–1.90 (m, 1 H) [2.42–2.32 (m, 1 H) for *Z*], 1.90–1.75 (m, 1 H) [2.52–2.42 (m, 1 H) for *Z*], 1.75–1.13 (m, 18 H). Anal. ($C_{13}H_{23}NO_3$) C, H, N.

1-(Nitromethyl)-4-methylcyclohexene oxide (10): yield 87%; bp 54–58 °C (0.04 Torr); trans/cis = 80/20; IR (neat) 1550, 1377, 1215 cm^{-1}; ^1H NMR δ 4.52 (d, *J* = 12.8 Hz, 1 H) [4.50 (d, *J* = 12.8 Hz, 1 H) for cis], 4.24 (d, *J* = 12.8 Hz, 1 H) [4.32 (d, *J* = 12.8 Hz, 1 H) for cis], 3.23 (br s, 1 H) [3.19 (br s, 1 H) for cis], 2.38–1.79 (m, 3 H), 1.79–1.20 (m, 4 H), 0.91 (d, *J* = 5.3 Hz, 3 H). Anal. ($C_8H_{13}NO_3$) C, H, N.

1-(Nitromethyl)cyclohexen-4-one oxide ethylene acetal (12): yield 81%; IR (neat) 1555, 1376 cm^{-1}; ^1H NMR δ 4.56 (d, *J* = 12.8 Hz, 1 H), 4.46 (d, *J* = 12.8 Hz, 1 H), 4.00–3.86 (m, 4 H), 3.23 (t, *J* = 3.0 Hz, 1 H), 2.32–2.16 (m, 2 H), 2.13 (d, *J* = 3.0 Hz, 2 H), 1.74–1.60 (m, 1 H), 1.58–1.48 (m, 1 H); ^{13}C NMR δ 105.9, 81.2, 64.5, 64.1, 56.7, 56.1, 34.2, 27.7, 23.8. Anal. ($C_9H_{13}NO_5$) C, H, N.

1-(Nitromethyl)-3,4-dihydronaphthalene oxide (16): yield 75%; IR (neat) 1552, 1490, 1432, 1372, 1312 cm^{-1}; ^1H NMR δ 7.70–6.88 (m, 4 H), 5.39 (d, *J* = 14.0 Hz, 1 H), 4.56 (d, *J* = 14.0 Hz, 1 H), 3.82 (d, *J* = 3.3 Hz, 1 H), 3.08–2.20 (m, 4 H), 2.19–1.68 (m, 2 H); ^{13}C NMR δ 137.1, 130.4, 129.2, 128.9, 126.6, 126.0, 61.8, 54.1, 25.0, 21.5. Anal. ($C_{11}H_{11}NO_3$) C, H, N.

(*E*)- and (*Z*)-1-nitro-2-phenyl-2-butene oxide (18): yield 85%; bp 77–81 °C (0.05 Torr); *E*/*Z* = 1/1; IR (neat) 1560, 1545, 1492, 1442, 1412, 1375 cm^{-1}; ^1H NMR δ 7.39 (br s, 5 H), 5.02 (d, *J* = 14.1, 1 H) and 4.80 (d, *J* = 14.1 Hz, 1 H) [4.96 (d, *J* = 13.2 Hz, 1 H) and 4.64 (d, *J* = 13.2 Hz, 1 H)], 3.23 (q, *J* = 5.3 Hz, 1 H) [3.42 (q, *J* = 5.3 Hz, 1 H)], 1.08 (d, *J* = 5.3 Hz, 3 H) [1.55 (d, *J* = 5.5 Hz, 3 H)]. Anal. ($C_{10}H_{11}NO_3$) C, H, N.

(*E*)- and (*Z*)-1-nitro-2-methyl-4-phenyl-2-butene oxide (20): yield 80%; bp 112–118 °C (0.03 Torr); *E*/*Z* = 71/29; IR (neat) 1557, 1495, 1452, 1375 cm^{-1}; ^1H NMR δ 7.23–7.36 (m, 5 H), 4.53 (d, *J* = 12.8 Hz, 1 H) and 4.32 (d, *J* = 12.8 Hz, 1 H) [4.67 (d, *J* = 13.2 Hz, 1 H) and 4.57 (d, *J* = 13.2 Hz, 1 H) for *Z*], 3.21 (t, *J* = 6.1 Hz, 1 H) [3.20 (dd, *J* = 4.5, 7.7 Hz, 1 H) for *Z*], 2.93 (d, *J* = 6.1 Hz, 2 H) [3.04 (dd, *J* = 4.5, 14.9 Hz, 1 H) and 2.88 (dd, *J* = 7.7, 14.9 Hz, 1 H) for *Z*], 1.59 (s, 3 H) [1.51 (s, 3 H) for *Z*]. Anal. ($C_{11}H_{13}NO_3$) C, H, N.

General Procedure for Transformation of β,γ-Epoxy Nitro Compounds into γ-Keto Sulfides. To a solution of PhSNa (0.528 g, 4 mmol) or a mixture of PhSH (0.441 g, 4 mmol) and Et_3N (0.202 g, 2 mmol) in DMF (5 mL) was added the β,γ-epoxy nitro compounds (2 mmol). The combined mixture was stirred at 25 or 70 °C for the stated period of time (see Table I and eq 3–10). The reaction mixture was partitioned between ether and water, and the aqueous phase was extracted with ether (3 × 30 mL). The combined ether extracts were washed with brine (3 × 30 mL) and water (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude products obtained in this manner could be purified by column chromatography (9:1 hexane–ethyl acetate).

2-((Phenylthio)methyl)cyclopentanone (9a):[10a] IR (neat) 1739, 1587, 1484, 1442 cm^{-1}; ^1H NMR δ 7.48–7.04 (m, 5 H), 3.44 (dd, *J* = 3.0, 12.7 Hz, 1 H), 2.76 (dd, *J* = 12.7, 8.8 Hz, 1 H), 2.56–1.44 (m, 7 H); ^{13}C NMR δ 218.6, 136.0, 129.4, 129.0, 126.2, 48.8, 38.1, 34.0, 29.3, 20.4.

2-((Phenylthio)methyl)cyclohexanone (9b): IR (neat) 1710, 1580, 1478, 1435 cm^{-1}; ^1H NMR δ 7.37–7.13 (m, 5 H), 3.48 (dd, *J* = 4.7, 13.4 Hz, 1 H), 2.73 (dd, *J* = 8.1, 13.4 Hz, 1 H), 2.60–2.49 (m, 1 H), 2.48–2.37 (m, 2 H), 2.36–2.24 (m, 1 H), 2.14–2.02 (m, 1 H), 1.94–1.84 (m, 1 H), 1.71–1.60 (m, 2 H), 1.49–1.34 (m, 1 H); ^{13}C NMR δ 211.1, 136.8, 129.0, 128.9, 125.9, 50.4, 42.0, 33.4, 27.8, 25.0. Anal. ($C_{13}H_{16}OS$) C, H.

2-((Phenylthio)methyl)cycloheptanone (9c): IR (neat) 1710, 1582, 1480, 1440 cm^{-1}; ^1H NMR δ 7.40–7.00 (m, 5 H), 3.38 (dd, *J* = 9.2, 16.2 Hz, 1 H), 2.76 (dd, *J* = 7.5, 16.2 Hz, 1 H), 2.88–2.60 (m, 1 H), 2.60–2.28 (m, 2 H), 2.28–1.12 (m, 8 H); ^{13}C NMR δ 213.9, 136.5, 129.5, 128.9, 126.1, 51.3, 43.5, 35.6, 30.6, 29.1, 28.8, 23.9. Anal. ($C_{14}H_{18}OS$) C, H.

2-((Phenylthio)methyl)cyclooctanone (9d): IR (neat) 1699, 1584, 1481, 1469, 1439 cm^{-1}; ^1H NMR δ 7.40–7.18 (m, 5 H), 3.30 (dd, *J* = 7.3, 12.3 Hz, 1 H), 3.01–2.93 (m, 1 H), 2.89 (dd, *J* = 6.3, 12.3 Hz, 1 H), 2.50–2.31 (m, 2 H), 2.08–1.92 (m, 2 H), 1.84–1.50 (m, 6 H), 1.46–1.33 (m, 1 H), 1.20–1.06 (m, 1 H); ^{13}C NMR δ 217.8, 136.2, 129.5, 128.9, 126.2, 49.0, 43.6, 35.7, 33.0, 27.8, 24.9, 24.7,

(13) It would be a mandatory requirement that the acidity of CH_2EWG in **3** is higher than that of the hydroxyl group.

24.3. Anal. ($C_{15}H_{20}OS$) C, H.

2-((Phenylthio)methyl)cyclododecanone (9e): IR ($CHCl_3$) 1703, 1583, 1481, 1470, 1440 cm^{-1}; ^1H NMR δ 7.45–7.18 (m, 5 H), 3.20 (dd, J = 7.5, 13.0 Hz, 1 H), 2.87 (dd, J = 6.9, 13.0 Hz, 1 H), 2.89–2.80 (m, 1 H), 2.80–2.70 (m, 1 H), 2.39–2.28 (m, 1 H), 1.94–1.74 (m, 3 H), 1.64–1.47 (m, 1 H), 1.40–1.10 (m, 14 H); ^{13}C NMR δ 212.4, 136.2, 129.8, 129.0, 126.3, 50.9, 38.3, 34.4, 29.0, 26.2, 26.0, 24.1, 23.7, 23.4, 22.4, 21.9, 21.8. Anal. ($C_{19}H_{28}OS$) C, H.

2-((Phenylthio)methyl)-5-methylcyclohexanone (11): trans/cis = 81/19; IR (neat) 1706, 1584, 1482, 1438 cm^{-1}; ^1H NMR δ 7.32–7.10 (m, 5 H), 3.45 (dd, J = 4.6, 13.4 Hz, 1 H) [3.36 (dd, J = 5.2, 13.1 Hz, 1 H) for cis], 2.69 (dd, J = 8.0, 13.4 Hz, 1 H) [2.79 (dd, J = 8.2, 13.4 Hz, 1 H) for cis], 2.55–2.08 (m, 3 H), 2.03–1.53 (m, 3 H), 1.34 (m, 2 H), 0.99 (d, J = 6.1 Hz, 3 H) [0.94 (d, J = 7.0 Hz, 3 H) for cis]. Anal. ($C_{14}H_{18}OS$) C, H.

2-((Phenylthio)methyl)-1,5-cyclohexanedione 5-(ethylene acetal) (13): IR (neat) 1708, 1584, 1482, 1440 cm^{-1}; ^1H NMR δ 7.14–7.35 (m, 5 H), 3.95 (m, 4 H), 3.51 (dd, J = 4.6, 13.7 Hz, 1 H), 2.73 (dd, J = 8.5, 13.7 Hz, 1 H), 2.63 (s, 2 H), 2.48 (m, 1 H), 2.32 (m, 1 H), 1.95 (m, 2 H), 1.53 (m, 1 H); ^{13}C NMR δ 206.2, 136.2, 129.0, 128.9, 126.0, 110.2, 64.8, 64.6, 51.4, 49.1, 34.3, 32.8, 26.4. Anal. ($C_{15}H_{18}O_3S$) C, H.

4-(Nitromethyl)-4-(phenylthio)-3-hydroxycyclohexanone ethylene acetal (14): ratio of two diastereomers (A vs B), 73:27; IR (neat) 3460 (br), 1550, 1477, 1440 cm^{-1}; ^1H NMR δ 7.67–7.27 (m, 5 H), 5.10 (d, J = 10.7 Hz, 1 H) [4.71 (d, J = 12.2 Hz, 1 H), for B], 4.32 (d, J = 10.7 Hz, 1 H) [4.54 (d, J = 12.2 Hz, 1 H) for B], 4.15 (m, 1 H), 3.97 (m, 4 H), 2.70–2.42 (m, 1 H), 2.37–2.05 (m, 2 H), 2.05–1.82 (m, 1 H), 1.75–1.58 (m, 3 H). Anal. ($C_{15}H_{19}O_5NS$) C, H, N.

3-(2-Hydroxyethoxy)-6-((phenylthio)methyl)-2-cyclohexen-1-one (15): IR ($CHCl_3$) 3430 (br), 1650, 1614, 1482, 1455 cm^{-1}; ^1H NMR δ 7.38–7.14 (m, 5 H), 5.37 (s, 1 H), 3.92 (m, 4 H), 3.70 (dd, J = 3.4, 13.4 Hz, 1 H), 2.78 (dd, J = 9.8, 13.4 Hz, 1 H), 2.52–2.40 (m, 2 H), 2.40–2.28 (m, 1 H), 2.20 (br, 1 H), 1.91–1.73 (m, 2 H); ^{13}C NMR δ 199.2, 177.3, 136.1, 128.9, 125.9, 102.5, 69.8, 60.4, 44.8, 35.6, 28.2, 25.7. Anal. ($C_{15}H_{18}O_3S$) C, H.

1-((Phenylthio)methyl)-2-oxo-1,2,3,4-tetrahydronaphthalene (17): IR (neat) 1710, 1579, 1478, 1440, 1434 cm^{-1}; ^1H NMR δ 7.40–7.08 (m, 5 H), 3.72 (dd, J = 5.2, 7.1 Hz, 1 H), 3.62 (dd, J = 5.2, 12.9 Hz, 1 H), 3.40 (dd, J = 7.1, 12.9 Hz, 1 H), 3.17 (dt, J = 15.6, 6.5 Hz, 1 H), 3.04 (dt, J = 15.6, 6.5 Hz, 1 H), 2.61 (t, J = 6.5 Hz, 2 H); ^{13}C NMR δ 210.1, 136.9, 136.2, 135.3, 129.5, 129.0, 127.9, 127.3, 126.9, 126.3, 52.6, 37.8, 35.2, 27.9. Anal. ($C_{17}H_{16}OS$) C, H.

1-(Phenylthio)-2-phenyl-3-butanone (19): IR (neat) 1710, 1595, 1580, 1490, 1476, 1450, 1433 cm^{-1}; ^1H NMR δ 7.39–7.16 (m, 5 H), 3.89 (dd, J = 6.3, 8.1 Hz, 1 H), 3.64 (dd, J = 8.05, 13.3 Hz, 1 H), 3.15 (dd, J = 6.3, 13.3 Hz, 1 H); ^{13}C NMR δ 206.4, 137.5, 136.2, 129.6, 129.1, 129.0, 128.2, 127.9, 126.3, 59.0, 35.7, 29.4. Anal. ($C_{16}H_{16}OS$) C, H.

1-(Phenylthio)-2-methyl-4-phenyl-3-butanone (21): IR (neat) 1710, 1583, 1495, 1480, 1453, 1438 cm^{-1}; ^1H NMR δ 7.33–7.10 (m, 5 H), 3.71 (s, 2 H), 3.19 (dd, J = 6.5, 12.4 Hz, 1 H), 2.92 (tq, J = 6.5, 7.0 Hz, 1 H), 2.84 (dd, J = 6.5, 12.4 Hz, 1 H), 1.16 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ 210.0, 136.0, 133.8, 133.0, 130.0, 129.1, 128.8, 127.2, 126.4, 49.5, 44.8, 36.7, 16.9. Anal. ($C_{17}H_{18}OS$) C, H.

1-Nitro-2-methyl-2-(phenylthio)-3-hydroxy-4-phenylbutane (22). The ratio of two diastereomers (A vs B) was 64:36.

A: IR (neat) 3550 (br), 1550, 1493, 1472, 1453, 1438, 1375, 900, 725 cm^{-1}; ^1H NMR δ 7.76–7.04 (m, 5 H), 4.66 (d, J = 12.9 Hz, 1 H), 4.50 (d, J = 12.9 Hz, 1 H), 3.86 (dd, J = 5.1, 10.3 Hz, 1 H), 3.40 (d, J = 13.6 Hz, 1 H), 2.64 (dd, J = 10.3, 13.6 Hz, 1 H), 2.34 (d, J = 5.1 Hz, 1 H), 1.33 (s, 3 H); ^{13}C NMR δ 138.5, 138.1, 137.9, 130.0, 129.4, 129.2, 128.7, 126.7, 81.0, 75.3, 54.8, 38.0, 19.5. Anal. ($C_{17}H_{19}NO_3S$) C, H, N.

B: IR ($CHCl_3$) 1550, 1495, 1455, 1438, 1372 cm^{-1}; ^1H NMR δ 7.74–7.00 (m, 5 H), 5.10 (d, J = 11.0 Hz, 1 H), 4.39 (d, J = 11.0 Hz, 1 H), 4.00 (m, 1 H), 3.04 (m, 2 H), 2.20 (d, J = 4.4 Hz, 1 H), 1.38 (s, 3 H); ^{13}C NMR δ 138.1, 130.0, 129.5, 129.2, 128.8, 126.9, 81.5, 75.4, 55.1, 38.3, 21.7. Anal. ($C_{17}H_{19}NO_3S$) C, H, N.

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Registry No. **7a**, 107454-82-0; **7b**, 107454-83-1; **7c**, 107454-84-2; **7d**, 107454-85-3; *cis*-**7e**, 107537-33-7; *trans*-**7e**, 107454-86-4; **9a**, 51679-33-5; **9b**, 51679-32-4; **9c**, 51679-34-6; **9d**, 124155-48-2; **9e**, 124155-49-3; **10** (isomer 1), 124223-44-5; **10** (isomer 2), 124155-35-7; *cis*-**11**, 124155-31-3; *trans*-**11**, 124155-36-8; **12**, 124155-37-9; **13**, 124155-38-0; *cis*-**14**, 124155-33-5; *trans*-**14**, 124155-39-1; **15**, 124155-40-4; **16**, 124155-41-5; **17**, 124155-42-6; *trans*-**18**, 124155-43-7; *cis*-**18**, 124155-50-6; **19**, 124155-44-8; *trans*-**20**, 124155-45-9; *cis*-**20**, 124155-51-7; **21**, 124155-46-0; (*R**,*R**)-**22**, 124155-32-4; (*R**,*S**)-**22**, 124155-47-1; $NO_2CH_2C(Ph)=CHCH_3$, 124155-53-9; $PhCH_2CH=C(CH_3)CH_2NO_2$, 124155-54-0; 1-(nitromethyl)cyclopentene, 2562-42-7; 1-(nitromethyl)cyclohexene, 5330-61-0; 1-(nitromethyl)cycloheptene, 52315-51-2; 1-(nitromethyl)cyclooctene, 90608-54-1; 1-(nitromethyl)cyclododecene, 124155-34-6; 1-(nitromethyl)-4-methylcyclohexene, 90087-63-1; 1-(nitromethyl)-cyclohexen-4-one ethylene acetal, 124155-52-8; 1-(nitromethyl)-3,4-dihydronaphthalene, 104489-04-5.

A New and Efficient Approach to Macrocyclic Keto Lactones

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A new and efficient method for macrolactonization has been developed. The intramolecular nucleophilic displacement of chloride from the highly electrophilic α-chloro ketone moiety in **15** by a remote carboxylate nucleophile resulted in the clean formation of the 11-membered keto lactone **1**. Relatively high substrate concentrations (up to 18 mM) could be employed without formation of dimeric or oligomeric byproducts. The slow mixing of substrate and base was not required. This macrolactonization reaction was studied in various solvents at a number of substrate concentrations and reaction temperatures in order to evaluate its scope and limitations. A low-temperature Ti(III) ion/peroxide induced radical addition reaction has also been developed. The lowering of the reaction temperature from 0 °C to −78 °C consistently afforded a dramatic increase in product yield from such reactions. This lowering of the reaction temperature proved essential when the highly functionalized acetoxymethyl vinyl ketone was employed as the radical acceptor.

During the past 15 years, a plethora of macrocyclic lactones (macrolides) have been isolated from natural sources. Many of these have been found to possess important and potentially useful biological properties[1] or to

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