conclude that the most likely assignment of the 530-cm^{-1} band is to the bending motion.

With the 6-31G* basis set, a Mulliken population analysis yields net charges of −0.81, 0.69, −0.38, and 0.17, on the carbon, magnesium, chlorine, and hydrogen atoms, respectively.[16] These results indicate that the Mg–Cl bond of the CH_3MgCl species is intermediate between ionic and covalent in character. The lowest unoccupied molecular orbital (LUMO) of CH_3MgCl (which has a large contribution from the Mg 3s orbital) lies at relatively low energy, drops quickly in energy with R–Mg–Cl bending, and is bound (i.e., acquires a negative energy) for angles less than about 145°. In the interaction of a Grignard reagent with a carbonyl group, we therefore expect that the interaction of the LUMO of the RMgX molecule and the π orbital of the carbonyl group, which is localized on the oxygen atom, becomes even more favorable by the adoption of a bent structure by the Grignard reagent.

Acknowledgment. This research was supported by the National Science Foundation. The calculations were performed with the Chemistry Department's Harris 800 minicomputer and the University's DEC 10/99. We thank Professor W. Hehre for a copy of the GAUSSIAN 82 program and for helpful suggestions.

Registry No. CH_3Cl, 74-87-3; CH_3MgCl, 676-58-4.

(16) A similar population analysis has been reported by Ratner et al. (Ratner, M. A.; Moskowitz, J. W.; Topiol, S. *J. Am. Chem. Soc.* **1978**, *100*, 2329). These authors utilized a pseudopotential procedure, treating explicitly only the valence electrons.

Sulfoximine-Mediated Resolutions of Ketones

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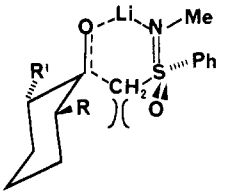
The importance of ketones in organic syntheses and their occurrence as biologically interesting molecules provide impetus to develop new methodologies for their resolutions. Optical resolution of ketones remains a problem lacking a practical and general solution.[1] The four approaches that have been taken for the optical activation of ketones are (1) modification of the carbonyl functionality (e.g., reduction to alcohol) to permit classical resolution,[2] (2) utilization of a carbonyl-specific resolving agent, e.g., "menthydrazide",[3] (3) chromatographic separation of racemates using resolved column packing,[4] and (4) asymmetric synthesis.[5] In this communication we describe a new ketone resolution technique based on the addition of an optically pure sulfoximine to selected, but important, classes of ketones.

We have found that the addition of **1**[6] as the α-lithio derivative **2** to ketones occurs readily and irreversibly (kinetic control) at −78 °C to give adducts **3** in excellent yields. Thermolysis of these adducts occurs smoothly in the temperature range 80–120 °C to regenerate the ketone and sulfoximine **1** (Scheme I). This extraordinarily facile C–C bond cleavage is undoubtedly related to the stability of the primary leaving group, ylide **4**, the *N*,*N*-dimethyl analogue of which is known to be one of the most stable of monosubstituted carbanions.[7]

Application of the chemistry depicted in Scheme I to the resolution of a chiral steroidal ketone using (−)-(*R*)-**1** is illustrated in Scheme II. As is readily apparent, such resolutions will be greatly simplified in those ketones that exhibit diastereoface specificity in the addition of **2** as this will limit the diastereomeric adducts to be separated to two. (Note that a new chiral center is generated at the original carbonyl site.) The resolution is also dependent on the separability of the adducts. It has been our experience that β-hydroxysulfoximines are highly responsive to separation by chromatography.[8]

A selection of results using this sulfoximine-mediated resolution technique is summarized in Table I. Several points are worthy of note. Envelope-shaped bicyclic ketones give the expected diastereoface specificity in the addition of **2**. Simple 2-substituted cyclohexanones were generally found to give rise to three diastereomeric adducts—two major adducts resulting from equatorial addition and a single minor product resulting from axial addition. An examination of Dreiding models reveals that the transition states for addition (assuming lithium coordination to the nitrogen and keto oxygen) are sterically unhindered from the equatorial face. Steric complications arise during axial attack, but with only one of the two diastereomeric transition states. The diastereoface



axial diastereomer, I, R′ = H, R / S=O interaction
axial diastereomer, II, R = H, no R′ / S=O interaction

selectivity of chiral acyclic ketones (or aldehydes) is usually low, and four diastereomers result from the addition of **2**. This situation can be improved when chelation control is possible.[9] The addition of the magnesium derivative of **1** to 2-methoxy-1,2-diphenylethanone resulted in only two diastereomers, albeit in rather low yield. The addition of **2** resulted in three diastereomers but in excellent yield.

The overall method is rather straightforward but a few technical details should be noted. In the addition step the reaction mixtures were maintained at −78 °C with stirring for 0.5–1 h prior to pouring the *cold* mixtures into aqueous ammonium chloride and extracting with diethyl ether. Chromatographic separations of the diastereomeric adducts were achieved by medium-pressure or flash liquid chromatography over silica gel with mixtures of ethyl acetate and hexanes. Thermolyses of the adducts were achieved, in the case of volatile ketones, by placing the purified diastereomers, without solvent, in a Kuglerohr tube under vacuum in an oven preset to ca. 120 °C. The thermolysis products distilled as they were formed. Adducts of nonvolatile ketones were thermolyzed (a) in refluxing 2-butanol (bp 98 °C) until TLC indicated complete reaction or (b) neat under argon at 130 °C for 5–10 min. Separation of the sulfoximine from the ketone was accomplished by extraction of the sulfoximine into aqueous mineral acid or aqueous $Cu(NO_3)_2$ solution or by percolation of the mixture through a short bed of silica gel (sulfoximine retained). The sulfoximines can be recovered in an unchanged state of optical purity and recycled.

A significant advantage inherent in this method is the rapidity with which the ultimate success of a resolution can be predicted.

(1) For reviews see: Wilen, S. H. In "Topics in Stereochemistry"; Eliel, E. L., Allinger, N. L., Eds.; Wiley-Interscience: New York, 1971; Vol. 6, p 107. Wilen, S. H. "Tables of Resolving Agents and Optical Resolutions"; University of Notre Dame Press: Notre Dame, IN, 1972. Boyle, P. H. *Quart. Rev.* **1971**, *25*, 323.
(2) For example see: Macbeth, A. K.; Mills, J. A. *J. Chem. Soc.* **1947**, 205.
(3) Woodward, R. B.; Kohman, T. P.; Harris, G. C. *J. Am. Chem. Soc.* **1941**, *63*, 120.
(4) Hesse, G.; Hagel, R. *Justus Liebigs Ann. Chem.* **1976**, 996.
(5) Meyers, A. I.; Williams, D. R.; Dreulinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032.
(6) Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424. Optically pure **1** exhibits $[\alpha]^{25}_D$ 184° (*c* 3, acetone).
(7) Bordwell, F. G.; Branca, J. C.; Johnson, C. R.; Vanier, N. R. *J. Org. Chem.* **1980**, *45*, 3884.
(8) Johnson, C. R.; Stark, C. J., Jr. *J. Org. Chem.*, in press.
(9) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, 1031.

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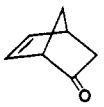
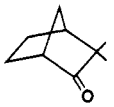
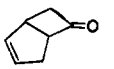
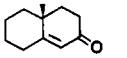
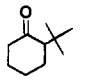
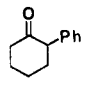
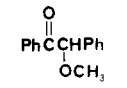
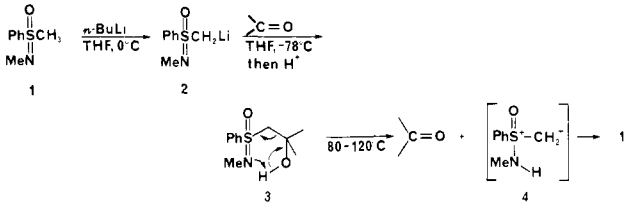
Table I. Results of the Sulfoximine-Mediated Ketone Resolution

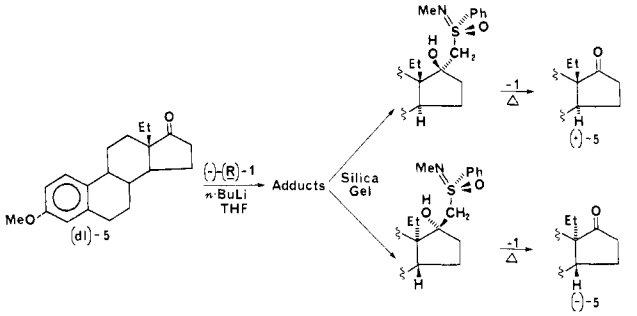
ketone	yield of addition, %	composition, %[a]	yield of diastereomer,[b] %	yield of thermolysis, %	$[\alpha]_D$ (temp (°C), concn, solvent),[c] deg	concn, solvent),[c] deg
	90	I 50 II 50	44 35	 50[d]	−1135.7 (28, 0.7, $CHCl_3$)[e]	592 (28, 1.7, $CHCl_3$)[f]
	94	I 50 II 50	47 47	80	−63.2 (20, 1, C_6H_6)	−61.2 (19, ns, C_6H_6)[g]
	98	I 50 II 50	25 23	80 98	−64.3 (25, 0.64, $CHCl_3$)[h] +59.6 (25, 1.3, $CHCl_3$)[h]	
	91	I 55 II 45	42 21	98 84	−207.0 (24, 1, EtOH)[h] +208.3 (24, 1, EtOH)[h]	+25 (ns, 1, EtOH)[i]
5	96	I 55 II 45	52 40	86 61	+106.4 (25, 1, 1:1 MeOH/$CHCl_3$) −104.4 (25, 1, 1:1 MeOH/$CHCl_3$)	−102.5 (25, 1, 1:1 MeOH/$CHCl_3$)[j]
	98	I 61 II 22 III 17	56 12 20	93 98 73	+36.0 (24.5, 1, MeOH)[b] −35.3 (24.5, 1, MeOH)[h] −35.4 (24.5, 1, MeOH)[h]	
	98	I 57 II 25 III 18	38 17 29	94 81 88	+112.5 (26, 0.6, C_6H_5) −59.3 (26, 0.6, C_6H_6) −112.0 (26, 0.6, C_6H_6)	+114.7° (25, 0.45, C_6H_6)[k]
	98	I 50 II 10 III 40	38 8 31	96 93	+52.8 (19, 0.6, C_6H_6) −51.5 (20, 0.6, C_6H_6)	+50.9 (15, 0.6, C_6H_6)[l]

[a] Determined by HPLC analysis (silica gel with EtOAc/hexane); numerals I, II, and III indicate the eluction order of the diastereomers. [b] After chromatography, % yield of pure diastereomer. [c] Concentration given in g/100 mL; ns = not specified. [d] Low yield due to loss of volatile ketone. [e] Sulfoximine of 95% ee was employed; rotations of ketones are not adjusted. [f] Literature value reported for material determined to be 48% optically pure: Mislow, K.; Berger, J. G. *J. Am. Chem. Soc.* 1962, *84*, 1956. Sandman, D. J.; Mislow, K. *J. Org. Chem.* 1968, *33*, 2924. [g] Huchel, H. *Justus Liebigs Ann. Chem.* 1941, *549*, 168. [h] Sulfoximine of 99% ee employed; rotations of ketones are not adjusted. [i] Adams, W. R.; Chapman, O. L.; Sieja, J. B.; Welstead, W. J. *J. Am. Chem. Soc.* 1966, *88*, 162. [j] Smith, H.; Hughes, G. A.; Douglas, G. H.; Wendt, G. R.; Buzby, B.; Hartley, D.; Herbst, D.; Jansen, A. B. A.; Ledig, K.; McLaughlin, B. J.; McMenamin, J.; Pattison, T. W.; Phillips, P. C.; Rees, R.; Siddall, J.; Siuda, J.; Smith, L. L.; Tokolics, J.; Watson, D. H. P. *J. Chem. Soc.* 1964, 4472. [k] Berli, G. *J. Chem. Soc. C* 1971, 3371. [l] Wren, H. *J. Chem. Soc.* 1909, 1583.

Scheme I



Scheme II



Chromatographic examination (TLC or HPLC on silica gel) of a small-scale addition of racemic **1** to racemic ketone,[10] optically pure **1** to racemic ketone, or racemic **1** to an optically pure ketone will reveal number and separability of the various diastereomers. We have found that, on a preparative scale, separations are feasible whenever the separation of the major diastereomers corresponds to an α value ≥ 1.25.

As implied above, the method has reciprocity,[11] and a number of ketones, particularly *l*-menthone, have been utilized to resolve (*dl*)-**1**.[12]

Acknowledgment. This research was supported by a grant from the National Science Foundation. We thank the Lubrizol Foundation for a fellowship for J.R.Z. and Dr. John Carson of Wyeth Laboratories for a gift of racemic **5**.

Registry No. (±)-(*R*)-**1**, 80482-67-3; (*dl*)-**5**, 968-74-1; (±)-**5**, 848-04-4; (−)-**5**, 17092-07-8; (±)-bicyclo[2.2.1]hept-5-en-2-one, 51736-74-4; (±)-3,3-dimethylbicyclo[2.2.1]hept-2-one, 52363-25-4; (±)-bicyclo-

(10) This assumes that complete mutual kinetic resolution does not obtain, in which case a single diastereomer would be formed. For an example where very high mutual kinetic resolution obtains see: Johnson, C. R.; Meanwell, N. A. *J. Am. Chem. Soc.* **1981**, *103*, 7667.

(11) It has been demonstrated that 1,3-dithiane 1-oxide can be resolved by separation of its (+)-camphor adducts followed by base-catalyzed cleavage. In principle, ketones could be resolved by using optically active 1,3-dithiane 1-oxide (Bryan, R. F.; Carey, F. A.; Dailey, O. D., Jr.; Maker, R. J.; Miller, R. W. *J. Org. Chem.* **1978**, *43*, 90).

(12) Stark, C. J., Jr. Ph.D. Dissertation, Wayne State University, Detroit, MI, 1978. Zeller, J. R. Ph.D. Dissertation, Wayne State University, Detroit, MI, 1981.

[3.2.0]hept-2-en-6-one, 62182-73-4; (±)-4,4a,5,7,8-hexahydro-4-methyl-2(3*H*)-naphthalenone, 40573-28-2; (±)-2-(*tert*-butyl)cyclohexanone, 13495-19-7; (±)-2-phenylcyclohexanone, 55700-93-1; (±)-1,2-diphenyl-2-methoxyethanone, 5987-95-1.

INOC Route to Carbocyclics: A Formal Total Synthesis of (±)-Sarkomycin

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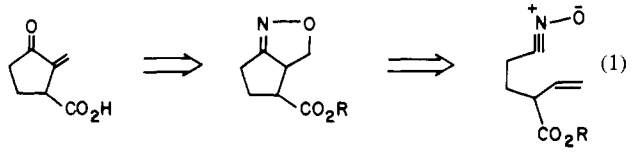
Received March 29, 1982

Although the intramolecular nitrile oxide cycloaddition (INOC) reaction has now found a wealth of applications in the synthesis of heterocyclic and alkaloid systems,[1] its use in the construction of cycloalkanones has been virtually unexplored.[2] In order to test its utility in the arena of five-membered ring synthesis and thus to provide the initial touchstone for investigations in this area, we decided to explore an INOC-based approach to the structurally simple antitumor agent sarkomycin (eq 1).[3]



(1)

Sarkomycin

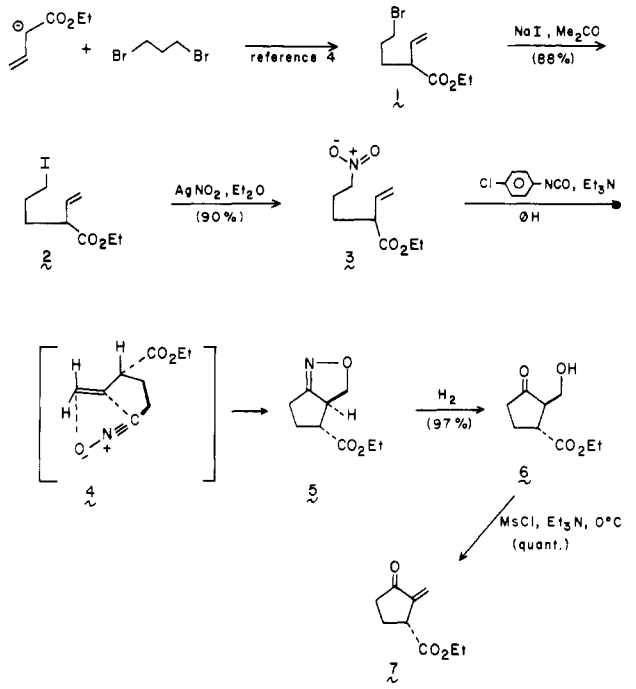
The anion of ethyl crotonate was thus generated by LDA/HMPA treatment and alkylated with the bis-electrophile 1,3-dibromopropane as described by Schlessinger.[4]

Bromide **1** was converted to its corresponding iodide **2** by stirring with 5 equiv of sodium iodide in acetone. While the reaction of **1** with silver nitrite in ether was sluggish, the iodide **2** reacted readily to provide the nitroalkene **3** of sufficient purity (VPC analysis) for use directly in the next reaction (Scheme I).[5]

Nitroalkene **3** was then reacted with excess *p*-chlorophenyl isocyanate[6] and a catalytic amount of triethylamine in benzene at room temperature. The transient nitrile oxide was intercepted by the tethered olefin to deliver a single isoxazoline **5** in 55% yield after column chromatography.

The fact that **5** suffered no change when exposed to DBU in methanol and that **6** (vide infra) exhibited no tendency to lactonize provides evidence for the stereochemistry depicted in **5**. This stereochemistry is presumed to arise from reaction through that transition state (see **4**) that minimizes $A^{1,3}$ strain. It may, of course, be argued that any of the other isomer [cis arrangement of the C-2 and C-3 substituents (sarkomycin numbering)] formed during the INOC reaction could have undergone epimerization

Scheme I



to **5** due to the presence of the amine catalyst. We believe, however, that the transition-state reasoning probably accounts for the production of **5** as the major *primary* product, for allylic strain has been shown to operate in related systems with a methyl group (a nonepimerizable center) substituting for a carboethoxy group.[7]

Isoxazoline **5** was now transformed to a β-hydroxy ketone by hydrogenation over freshly prepared W-2 Raney nickel in a 5:1 mixture of methanol and water containing 3 equiv of acetic or boric acid.[8] Subjection of the crude 2-(hydroxymethyl)cyclopentanone derivative **6** to mesyl chloride and triethylamine in methylene chloride at 0 °C afforded in quantitative yield the 2-methylenecyclopentanone **7**. Since **7** has been converted by Toki to sarkomycin,[3] the obtention of this compound completes the formal total synthesis of the natural product.

The work reported herein demonstrates in the context of a total synthesis the ability of the isoxazoline ring to function as a masked α,β-unsaturated ketone.[9] This synthesis does thus herald a conceptually new approach to the construction of functionalized

† Alfred P. Sloan Fellow, 1978–1982; Camille and Henry Dreyfus Teacher Scholar, 1982–1987.

‡ Andrew Mellon Predoctoral Fellow of the University of Pittsburgh, 1981–1983.

(1) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Simoni, D.; Guarneri, M.; Gandolfi, C. *J. Org. Chem.* **1980**, *45*, 3141. Kozikowski, A. P.; Ishida, H. *J. Am. Chem. Soc.* **1980**, *102*, 4265. Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskoković, M. R. *Ibid.* **1978**, *100*, 6291. Stevens, R. V.; Christensen, C. G.; Cory, R. M.; Thorsett, E. *Ibid.* **1975**, *97*, 5940. Kametani, T.; Huang, S.-P.; Ihara, M. *Heterocycles* **1979**, *12*, 1183.

(2) For an exception, see: Wollenberg, R. H.; Goldstein, J. E. *Synthesis*, **1980**, 757.

(3) Umezawa, H.; Takeuchi, T.; Nitta, K.; Yamamoto, T.; Yamaoka, S. *J. Antibiot., Ser. A* **1953**, *6*, 101. Toki, K. *Bull. Chem. Soc. Jpn.* **1957**, *30*, 450. Toki, K. *Ibid.* **1958**, *31*, 333. Marx, J. N.; Minaskanian, G. *Tetrahedron Lett.* **1979**, 4175. Boeckman, R. K., Jr.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752. Kobayashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 4295.

(4) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

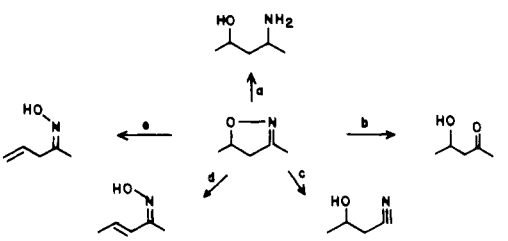
(5) Kornblum, N.; Ungnade, H. E. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 724.

(6) The *p*-chlorophenyl isocyanate was employed instead of phenyl isocyanate in order to facilitate separation of the isoxazoline from the urea byproduct.

(7) Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.* **1982**, *23*, 2081.

(8) The reduction conditions employing boric acid were developed by Professor D. P. Curran. We thank him for informing us of this modification. See: Curran, D. P., following communication. For other examples of the conversion of isoxazolines to β-hydroxy ketones by hydrogenation, see: Asaoka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 735. See also ref 2. Hydrogenolysis with Raney nickel/aluminum chloride and ozonolysis will convert isoxazolines to β-hydroxy ketones without loss of stereochemistry: Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.*, in press.

(9) The isoxazoline ring system proves to be a very versatile heterocycle, for it can be manipulated to provide access to (a) γ-amino alcohols [Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248. Jäger, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3129. Jäger, V.; Buss, V.; Schwab, W. *Ibid.* **1978**, 3133], (b) β-hydroxy ketones [this paper and ref 8], (c) β-hydroxy nitriles, acids, and esters [Moersch, G. W.; Wittle, E. L.; Neuklis, W. A. *J. Org. Chem.* **1967**, *32*, 1387. Kozikowski A. P.; Adamczyk, M. *J. Org. Chem.*, submitted], (d) α,β- and (e) β,γ-unsaturated oximes [Jäger, V.; Grund, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 50. Jäger, V.; Grund, H.; Schwab, W. *Ibid.* **1979**, *18*, 78].



0002-7863/82/1504-4023$01.25/0