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

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

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Although the intramolecular nitrile oxide cycloaddition (INOC) reaction has now found a wealth of applications in the synthesis of heterocyclic and alkaloid systems, <sup>1</sup> its use in the construction of cycloalkanones has been virtually unexplored.<sup>2</sup> 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).<sup>3</sup>

## 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.<sup>4</sup>

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).

Nitroalkene 3 was then reacted with excess p-chlorophenyl isocyanate<sup>6</sup> 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<sup>1,3</sup> 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

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

(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.

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.<sup>7</sup>

Isoxazoline 5 was now transformed to a  $\beta$ -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. 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, 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  $\alpha,\beta$ -unsaturated ketone. This synthesis does thus herald a conceptually new approach to the construction of functionalized

(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)  $\gamma$ -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)  $\beta$ -hydroxy ketones [this paper and ref 8], (c)  $\beta$ -hydroxy itriles, 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)  $\alpha,\beta$ - and (e)  $\beta,\gamma$ -unsaturated oximes [Jäger, V.; Grund, H. Angew. Chem., Int. Ed. Engl. 1976, 15, 50. Jäger, V.; Grund, H.; Schwab, W. Ibid. 1979, 18. 78].

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<sup>&</sup>lt;sup>1</sup>Andrew Mellon Predoctoral Fellow of the University of Pittsburgh, 1981–1983.

<sup>(1)</sup> Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Simoni, D.; Guuarneri, 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.

<sup>(3)</sup> 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, 226

carbocyclics. Simple modifications in the above scheme should make it possible, for example, to utilize the INOC reaction in the construction of other cyclopentanoids (e.g., pentenomycin and the methylenomycins<sup>10</sup>). By a building of additional oxygen functionality into the nitroalkene, the synthesis of prostaglandins and prostaglandin analogues becomes equally feasible.<sup>11</sup>

Acknowledgment. We are indebted to the National Institutes of Health (Grant No. HL20579) for support of these investiga-

Registry No.  $(\pm)$ -1, 82065-11-0;  $(\pm)$ -2, 82065-12-1;  $(\pm)$ -3, 82065-13-2;  $(\pm)$ -5, 82065-14-3;  $(\pm)$ -6, 82065-15-4;  $(\pm)$ -7, 82080-50-0;  $(\pm)$ sarkomycin, 72581-31-8; p-ClC<sub>6</sub>H<sub>4</sub>NCO, 104-12-1.

(11) All new compounds reported herein gave satisfactory NMR, IR, and mass spectral data.

## Reduction of $\Delta^2$ -Isoxazolines: A Conceptually Different Approach to the Formation of Aldol Adducts

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The aldol reaction and related carbonyl condensations continue to be of fundamental importance in organic chemistry.<sup>2</sup> We now report a conceptually different approach to aldol adducts that involves cycloaddition, rather than carbonyl condensation, in the key carbon-carbon bond-forming reaction. The two-step sequence exploits the potential synthetic equivalency of  $\Delta^2$ -isoxazolines and  $\beta$ -hydroxy ketones as outlined in eq 1. Well-known cycloaddition

$$[CH_{3}C=N-O] \xrightarrow{R} \xrightarrow{R} \xrightarrow{N-O} \xrightarrow{R} \xrightarrow{H_{2}} \xrightarrow{NH} \xrightarrow{OH} \xrightarrow{CH_{3}CH_{2}NO_{2}} \xrightarrow{CH_{3}CH_{2}NO_{2}} \xrightarrow{NH_{2}OH} \xrightarrow{CH_{3}CH_{2}NO_{2}} \xrightarrow{NH_{2}CH_{3}NO_{2}} \xrightarrow{NH_{2}OH} \xrightarrow{CH_{3}CH_{2}NO_{2}} \xrightarrow{NH_{2}CH_{3}NO_{2}} \xrightarrow{NH_{2}CH_{3$$

of an in situ generated nitrile oxide 1 with a mono- or 1,1-disubstituted olefin typically produces the 5-substituted  $\Delta^2$ -isoxazoline 2 in high yield with complete regioselectivity.3 Although most of the previous conditions used to reduce  $\Delta^2$ -isoxazolines have resulted in complete reduction to the amino alcohol,4 we felt that supported metal-type catalysts should reduce the weak N-O bond first. In the presence of water, rapid hydrolysis of the labile hydroxyimine 3 should then occur.

Table I

en- try	isoxazoline <sup>a</sup>	con- di- tions	pro- duct	yield, <sup>b</sup>	% epimeri- zation <sup>c</sup>
	CH3 R2	CI	13	OH R <sub>1</sub>	3
1 2 3 4 5 6 7 8 9 10 11	2a $R_1 = R_2 = H$ ; $R_3 = n \cdot C_4 H_9$ 2a 2b $R_1 = R_2 = H$ , $R_3 = Ph$ 2c $R_1 = H$ ; $R_2 = CH_3$ ; $R_3 = n \cdot C_3 H_7$ 6a $R_1 = R_3 = CH_3$ ; $R_2 = H$ 6a 6a $R_1 = R_3 = n \cdot C_3 H_7$ , $R_2 = H$ 7a $R_1 = R_2 = CH_3$ ; $R_3 = H$ $R_1$ , $R_2 = (CH_2)_4$ ; $R_3 = H$ $R_1$ , $R_2 = (CH_2)_5$ ; $R_3 = H$	d e f g d e f f f f g g	4a 4a 4b 4c 8a 8a 8a	81 (90) 79 84 (88) (86) 83 79 77 87 (97)	9 6 <2 <2 <2 <2 <2 <2 <2
12 13 14 15 16 17 18 19 20 21	6b $n = 2$ ; $R_1 = H$ ; $R_2 = CH_3$ 6b $n = 2$ ; $R_1 = H$ ; $R_2 = Ph$ 6c $n = 1$ ; $R_1 = H$ ; $R_2 = CH_3$ 7b $n = 2$ ; $R_1 = CH_3$ ; $R_2 = H$ 7c $n = 2$ ; $R_1 = CH_3$ ; $R_2 = H$ 7c $n = 1$ ; $R_1 = CH_3$ ; $R_2 = H$ 7c $n = 2$ ; $R_1 = CH_3$ ; $R_2 = H$ 7c $n = 2$ ; $R_1 = CH_3$ ; $R_2 = H$	f g g g g f g g f g g	8b 8b 8c 9b 9c 9c 11	(92) 85 73 (84) (89) 90 74 (81) (86) 82	4 <2 <2 <2 <5 <2 <2 <5 <2 <5 <4 <5 <5 <4 <5 <5 <5 <5 <5 <5 <5 <5 <5 <5 <5 <5 <5

a Nitro olefins were prepared intentionally as a mixture of isomers via Wittig reaction. After cycloaddition, the isomers were separated by flash chromatography.  $^b$  Yields refer to isolated yield of product purified by recrystallization or evaporative distillation. Crude yields were generally above 90%. Yields in parentheses refer to crude product. <sup>c</sup> Diastereomeric ratios were determined by integration of the carbinol proton region in the expanded 300-MHz spectra of crude products. In most cases the ratios were confirmed by integration of other appropriate resonances. <sup>d</sup> NaOAc/HOAc buffer. <sup>e</sup> NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, buffer. <sup>f</sup> Catalytic Raney nickel, 15:1 MeOH/H<sub>2</sub>O, 2 equiv of B(OCH<sub>3</sub>)<sub>3</sub>, H<sub>2</sub> gas, 0.4-6 h, room temperature. g Catalytic Raney nickel, 5:1 MeOH/  $H_2O$ , 2-5 equiv of  $B(OH)_3$ ,  $H_2$  gas, 0.5-6 h, room temperature. h Due to absence of a carbinol proton resonance, a more accurate determination was not possible.

A survey of common catalysts6 using adduct 2a indicated that Raney nickel<sup>7</sup> (catalytic amount, 15:1 MeOH/H<sub>2</sub>O, 1 atm of H<sub>2</sub>) was most satisfactory. Thus 2a was reduced to 4a in 81% yield after evaporative distillation8 (see Table I, entry 1). The presence

<sup>(10)</sup> Umino, K.; Takeda, N.; Ito, Y.; Okuda, T. Chem. Pharm. Bull. 1974, 22, 1233. Haneishi, T.; Kitihara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. J. Antibiot. 1974, 27, 386. Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. Ibid. 1974, 27, 393. Hornemann, U.; Hopwood, D. A. Tetrahedron Lett. 1978, 2977.

<sup>(1)</sup> Recipient of a Dreyfus Foundation Grant for Newly Appointed Faculty

in Chemistry, 1981–1986.
(2) (a) Nielsen, A. T.; Houlihan, W. J. Org. React. 1968, 16, 1. House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 629-682. (b) Barco, A.; Bennetti, S.; Baraldi, R.; Guarmeri, M.; Pollini, G. P.; Simoni, O. J. Chem. Soc., Chem. Commun. 1981, 599.

<sup>(3)</sup> For an excellent review of the chemistry of nitrile oxides see: Grundmann, C.; Grünanger, P. "The Nitrile Oxides"; Springer-Verlag: New York,

<sup>(4)</sup> Jäger, V.; Buss, V.; Schwab, W. Tetrahedron Lett. 1978, 3133. Jäger, V.; Buss, V. Liebigs Ann. Chem. 1980, 101. Jäger, V.; Buss, V.; Schwab, W. Ibid. 1980, 122. Jäger, V.; Schwab, W.; Buss, V. Angew. Chem., Int. Ed. Engl. 1981, 20, 601. For reduction to aziridines see: Kotera, K.; Takano, Y.; Matsuura, A.; Kotahonoki, K. Tetrahedran 1970, 26, 539.

<sup>(5)</sup> Most recently, two isolated examples of this type of reduction have been published. (a) Wollenberg, R. H.; Goldstein, J. E. Synthesis 1980, 757. (b) Asoaka, M.; Mukuta, T.; Takei, H. Tetrahedron Lett. 1981, 22, 735. (c) The amino alcohol has also been oxidized to the hydroxy ketone. Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. J. Am. Chem. Soc. 1978, 100, 7069.

<sup>(6)</sup> Platinum oxide (MeOH, H2O, AcOH) produced the amino alcohol. Palladium on carbon (MeOH, H2O, HOAc) produced variable amounts of the hydroxy ketone and amino alcohol. Subsequently, we have found that reduction of 2a to 4a is cleanly accomplished by 10% Pd-C (MeOH, H<sub>2</sub>O, B(OH)<sub>3</sub>); however, the generality of these conditions has not been determined.

<sup>(7)</sup> Most of the reductions were performed with commercially available Ra-Ni (Alfa Inorganics), which was carefully washed free of hydroxide by repeated stirring with water and decantation (~20 times) and stored under MeOH. Subsequently, it was found that W-2 Ra-Ni (Mozino, R. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 181) was effective, with a faster reaction rate. This was also carefully washed free of hydroxide and stored under MeOH.

<sup>(8)</sup> Known β-hydroxy ketones exhibited spectra and physical data identical with those obtained from literature sources. New  $\beta$ -hydroxy ketones exhibited spectra consistent with proposed structures as well as satisfactory elemental analysis and/or high-resolution mass spectra.