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SYNTHETIC APPROACHES TO BICYCLOMYCIN I. PREPARATION OF MONOCYCLIC INTERMEDIATES BY RETROGRADE MICHAEL CLEAVAGE OF 6-ALKYL-6-METHOXYHEXAHYDRO-3H-THIAZOLO [3,4-a]PYRAZINE-5,8-DIONES.

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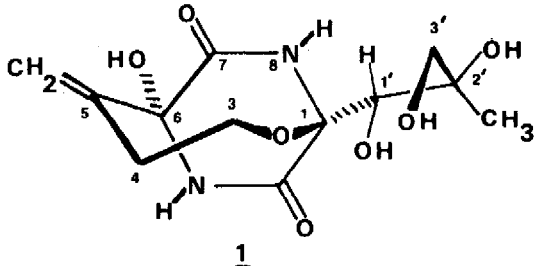
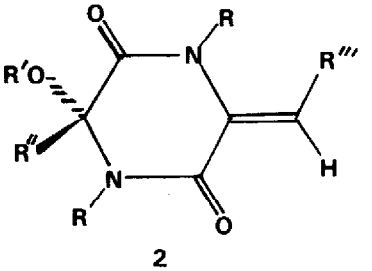
The syntheses of N-protected-3-(hydroxypropyl)-3-methoxy-6-alkylidine piperazine-2,5-diones are described, in relation to an approach to bicyclomycin. A chemoselective Grignard reaction and a novel diastereoselective retrograde Michael cleavage highlight the sequence.

In connection with a proposed total synthesis of bicyclomycin 1,[1] we have been investigating the preparation of alkoxy alkylidine piperazinediones of the type 2. Our strategy involved incorporation of the potential alkylidene into a second ring. The synthesis of



1

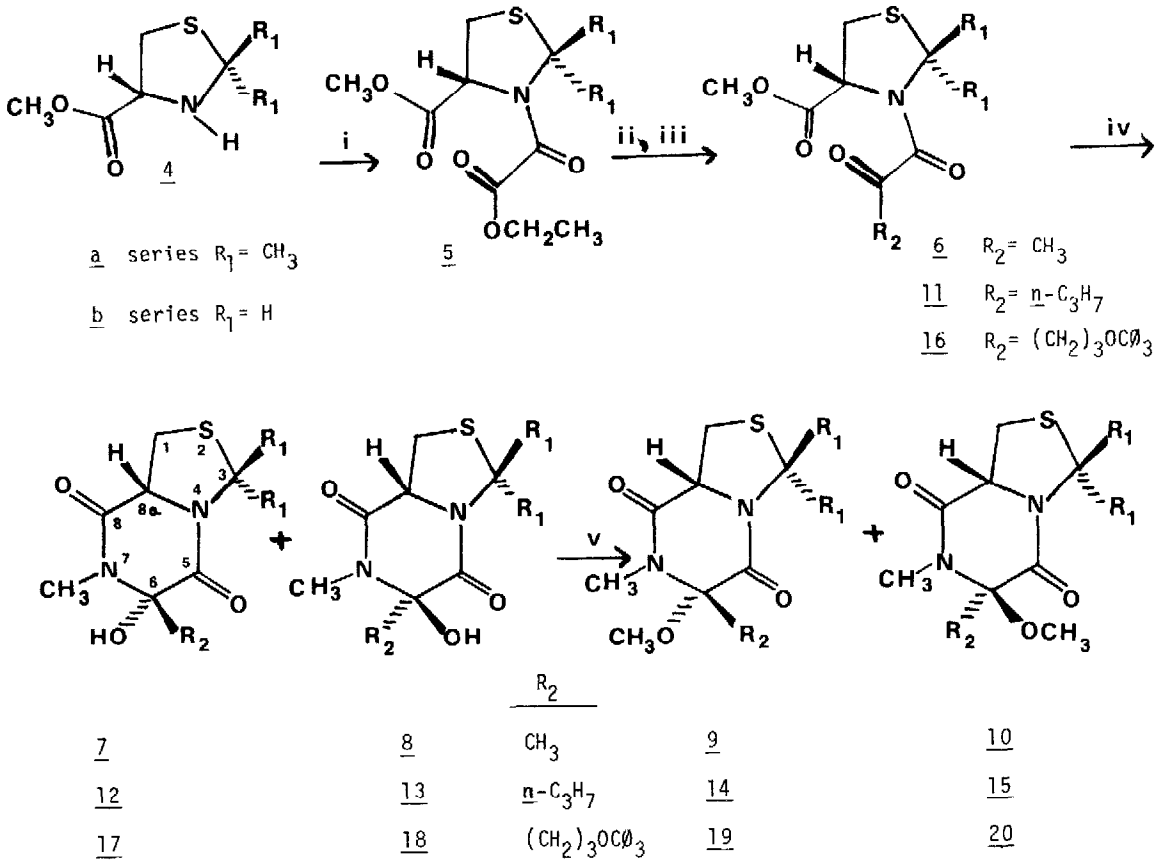


2

the N,N,O-trimethyl compound 3 from L-cysteine thiazolidine methyl ester 4, outlined in Scheme I, is illustrative of our approach.

Condensation of 4 with ethyl oxalate gave the oxamate thiazolidine 5 which was found to react with a variety of Grignard reagents by exclusive addition to the oxamate ester in excellent yield to afford compounds such as 6, 11, or 16. This chemoselectivity enabled a variety of substituted thiazolidine oxamates to be easily elaborated without preparation of the corresponding α-keto acids.[2] Reaction of these compounds with methylamine afforded the hydroxypiperazinediones 7+8, 12+13, and 17+18 which were converted to their corresponding methyl ethers 9+10, 14+15, and 19+20 using methyl iodide and silver oxide.[3]

Scheme I



4

a series R_1 = CH_3

b series R_1 = H

5

6 R_2 = CH_3

11 R_2 = n-C_3H_7

16 R_2 = $(CH_2)_3OC\emptyset_3$

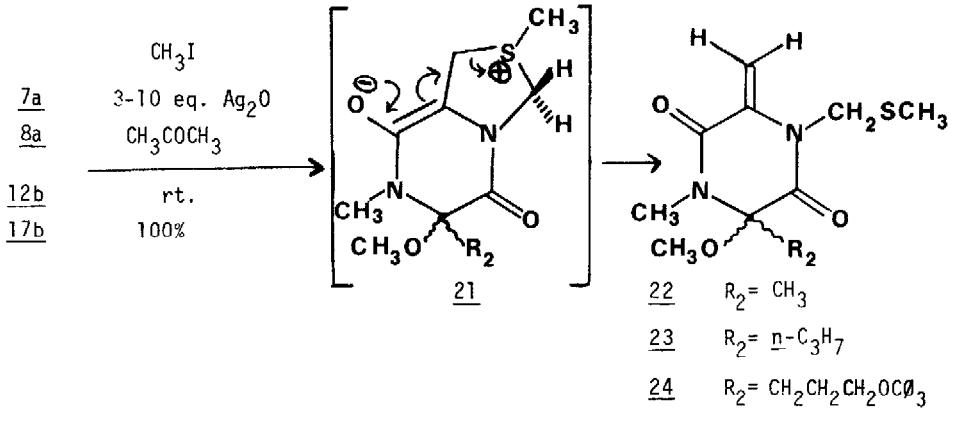
		R_2		
7	8	CH_3	9	10
12	13	n-C_3H_7	14	15
17	18	$(CH_2)_3OC\emptyset_3$	19	20

i) $HOC(=O)-C(=O)-OC_2H_5$, DCC, CH_2Cl_2, rt, 100%; ii) R_2MgBr, -78°, Et_2O, 3h; iii) 5N HCl, -40°, 85%; iv) CH_3NH_2, rt, 2 h, 65-90%; v) CH_3I, 1 eq. Ag_2O, DMF, 100%.

The stereochemical outcome of the amination of substrates such as 6, 11, and 16 in the a series is under kinetic control. Thus, after separation, 7a and 8a maintained their integrity when subjected to the reaction conditions.[4] The kinetic ratio of 7a and 8a was 2:1 at room temperature and 1:9 at -78°.[5] The amination of 11a and 16a, which have larger R_2 side chains, gave exclusively 12a and 17a respectively, and these products were also stable when resubjected to the reaction conditions. In the b series (R_1 = H) the major products were, as before, 7b, 12b, and 17b, respectively. However, in this series the products 7b and 8b, after separation, equilibrated to the original ratio when resubjected to the amination reaction. Typical epimer ratios were 7b:8b = 1.3:1 at -15°, 12b:13b = 4:1 at rt, and 17b:18b = 3:2 at room temperature.[6]

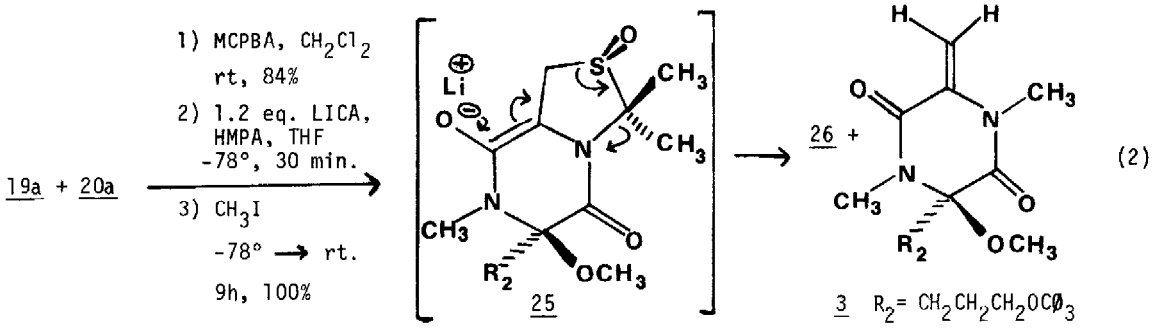
The stereoselectivity of the O-methylation also depended on both structure and reaction conditions. In the 3,3-dimethyl series, using 1.2 molar equivalents of silver oxide, methylation occured with predominant (60-80%) retention of the configurations at C-6 and C-8a. Typical epimer ratios at room temperature were 9a:10a = 2:1 from 7a, 9a:10a = 1:1.5 from 8a, 14a:15a = 2:1 from 12a, and 19a:20a = 4:1 from 17a. Methylation of the dihydro compounds 7b or 8b showed a stereoselectivity of 3:2 in favor of the product 10b, while methylation of 12b and 17b showed a 3:2 selectivity in favor of the products 14b and 19b (using 1.2 molar equivalents of silver oxide).[7]

Transformation of the thiazolidine ring into the exocyclic alkylidene moiety in the presence of the labile carbinolamide was readily accomplished by activating the thiazolidine sulfur toward a retrograde Michael reaction. Thiazolidines derived from formaldehyde (7b, 8b, 12b or 17b) were readily alkylated with methyl iodide on both the C-6 oxygen and on sulfur. The resulting enolates 21, formed by using excess molar equivalents of silver oxide in acetone, readily cleaved to give the thiomethyl ethers 22-24 as shown in equation 1.[8-10]



(1)

Thiazolidines derived from acetone were converted to their β sulfoxides followed by enolization and retrograde Michael cleavage to give, after quenching with methyl iodide, the N,N,O-trimethyl compound 3 in addition to complete recovery of the unreacted sulfoxide diastereomer 26 as shown in equation 2.[11] The unprecedented diastereoselectivity of this



(2)

retrograde Michael reaction is postulated to arise from lithium chelation with the methoxy group followed by syn intramolecular proton abstraction giving enolate 25 which, after retrograde Michael cleavage, underwent N-alkylation.[11]

Further investigation of these reactions and the cyclization studies on compound 3 are in progress.[12]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the ACS, for support of this research.

Notes and References.

1. a) H. Maag, J.F. Blount, D.L. Coffen, T.V. Steppe, and F. Wong, J. Am. Chem. Soc. 100, 6786 (1978); b) A. Someya, M. Iseki, and N. Tanaka, J. Antibiotics 32, 402 (1979); c) B.W. Muller, O. Zak, W. Kump, W. Tosch, and O. Wacker, ibid. 32, 689 (1979).

2. The chemoselectivity of Grignard addition to the ester end of oxamates was suggested by the method of M. Barre and M. Behal [Compt. Rend. 184, 825 (1927)] to prepare α- keto acids. The selectivity of the Grignard addition to the oxamate ester over the cysteine thiazolidine ester was predicted on the basis of electronic and steric factors. Alternatively the alkyl series 6 and 11 could be prepared by either direct coupling of 4 with each respective keto acid.

3. All compounds gave satisfactory spectral data. The assignment of relative stereochemistry is based primarily on nmr data (100 MHz, $CDCl_3$). For the two compounds 7b and 8b, the relative nmr values of the R_2 CH_3 groups correlated with the values of the corresponding proline analogs reported by J. Häusler and U. Schmidt [Chem. Ber. 107, 2804 (1974)].

4. Epimerization could occur by base catalyzed ring equilibration at C-6 or by enolization at C-8a.

5. These results suggest that there may be a temperature dependence on the s-cis, s-trans equilibrium of 6 and also a diastereoface differentiation of methylamine attack.

6. Circular dichroism studies do not unequivocally suggest which mode(s) of epimerization occured. The optical purity of a derivative of 3 will be determined.

7. Studies to increase this stereoselectivity are in progress. The base and solvent are more critical than the reaction temperature.

8. The β elimination of sulfur leaving groups from cysteine has been used to prepare dehydroamino acids.[9] The novelty of this approach lies in the fact that chemoselective eliminations of the sulfur leaving groups have been achieved in the presence of an extremely labile O-methyl carbinolamide moiety.

9. U. Schmidt, J. Häusler, E. Öhler, and H. Poisel, Fort. Prog. Chem. Org. Nat. Prod. 37, 251 (1979).

10. The corresponding O-methyl compounds such as 9b and 10b, did not cleave when resubjected to the cleavage reaction using excess silver oxide and methyl iodide in DMF or acetone.

11. The same diastereoselectivity was observed in the cleavage of the β sulfoxides of 9a and 10a, that is, the sulfoxide of 10a underwent retrograde Michael cleavage to give the R_2 = CH_3 analog of 3 while the sulfoxide of 9a was less reactive. L.V. Dunkerton and C.D. Juengst, unpublished results. For other examples of lithium alkoxy chelation see A.I. Meyers, et.al., J. Org. Chem. 44, 2250 (1979), and D. Enders, et.al., Chem. Ber. 112, 2933 (1979) and ref. therein.

12. Compound 3 will be used in cyclization studies directed towards model compounds in which C-6 of 3 will be C-6 of the bicyclic model of 1. This route is also illustrative of the preparation of analogs in which C-6 of 3 will be C-1 of another bicyclic model of 1.

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