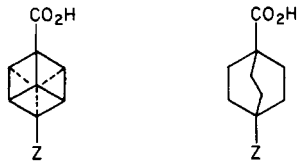
energy) in the case of longer chains.

This choice of a field mechanism for the electrostatic interaction in the present situation is consistent with current opinion on the nature of polar effects.[20] An important part of the evidence bearing on this matter comes from a comparison of substituent effects on the ionization of cubane- and bicyclo[2.2.2]octane-carboxylic acids.[21] When the substituents are situated in the 4 positions of these acids, as in **1** and **2**, the distance between them



1 **2**

and the carboxylic acid function is exactly the same (to within 0.1 Å) in the two series. In **1**, however, there are six (overlapping) three-bond pathways between Z and CO_2H, whereas in **2** there are only three such pathways. Field effects in the two series should therefore be the same, but inductive effects in **1** should be twice as strong as in **2**. It is found experimentally that substituent effects are actually the same in the two series, and this is taken as indication that the interaction occurs by a field rather than by an inductive mechanism.

This argument, however, loses some of its force if, instead of counting the number of equivalent bond pathways between the substituents in **1** and **2**, one regards the bonds as small capacitors of equal size, C. Application of the laws of electrical conduction then gives an equivalent capacitance of 6C/17 to an array with the shape of **1**, and an equivalent capacitance of 6C/18 to an array with the shape of **2**. The ratio of these results differs from unity by only 1 part in 18 or 6%, which is within experimental uncertainty the same as the unit ratio of substituent effects found in the two series of carboxylic acids **1** and **2**. With this interpretation of these effects, therefore, these data are just as consistent with the inductive as with the field interpretation of the polar effect.

The largest electrostatic effect found in the present study is the factor of 73 obtained in the detritiation of chloroform catalyzed by 3-trimethylammoniopropylamine. This amounts to a reduction in free energy of activation of 2.5 kcal mol^{-1}. If 5.0 Å is taken as the distance separating the positively charged nitrogen and negatively charged carbon atoms in the transition state of this reaction, application of Coulomb's law gives $\epsilon = 26$ as the effective dielectric constant of the medium surrounding these charges which is required to produce this energy reduction; this is not an unreasonable value.

Acknowledgment. We are grateful to Professor C. L. Perrin for stimulating discussion and the Natural Sciences and Engineering Research Council and the donors of the Petroleum Research Fund of the American Chemical Society for financial support.

Registry No. $(CH_3)_3N^+(CH_2)_3NH_2 \cdot Br^-$, 28841-49-8; $(CH_3)_3N^+(CH_2)_4NH_2 \cdot Br^-$, 30834-99-2; $(CH_3)_3N^+(CH_2)_5NH_2 \cdot Br^-$, 30835-02-0; $(CH_2OH)_3CNH_2$, 77-86-1; $(CH_2OH)_2C(CH_3)NH_2$, 115-69-5; $CH_2OH-CH_2NH_2$, 141-43-5; $CH_3(CH_2)_3NH_2$, 109-73-9; $(CH_3)_3CNH_2$, 75-64-9; $O_2CCH_2NH_2$, 23297-34-9; $O_2C(CH_2)_2NH_2$, 23297-31-6; $NH_2(CH_2)_2N-H_2$, 107-15-3; $NH_2(CH_2)_2NH_2 \cdot HCl$, 18299-54-2; $(CH_3)_3N^+(CH_2)_2NH_2 \cdot Br^-$, 53759-29-8; $(CH_3)_3N^+(CH_2)_3NH_2 \cdot Br^- \cdot HBr$, 33968-64-8; $(CH_3)_3N^+(CH_2)_4NH_2 \cdot Br^- \cdot HBr$, 33968-65-9; $(CH_3)_3N^+(CH_2)_5NH_2 \cdot Br^- \cdot HBr$, 33968-66-0; chloroform, 67-66-3; hydrogen, 1333-74-0; 2-nitropropane, 79-46-9.

Supplementary Material Available: Tables S1-S3 of rate constants (6 pages). Ordering information is given on current masthead page.

(20) For a recent review, see: Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley: New York, 1975; pp 38-45.

(21) Baker, F. W.; Parish, R. C.; Stock, L. M. *J. Am. Chem. Soc.* **1967**, *89*, 5677-5685.

Alkylation of Amino Acids without Loss of the Optical Activity: Preparation of α-Substituted Proline Derivatives. A Case of Self-Reproduction of Chirality[1,2]

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Contribution from the Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, ETH-Zentrum, CH-8092 Zürich, Switzerland. *Received January 26, 1983*

Abstract: Proline is condensed with pivalaldehyde to give a single stereoisomer of 2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**2**). This is deprotonated with LDA to give a chiral, nonracemic enolate (**3**), which combines with electrophiles such as D^+ (to **4**), the more reactive alkylating reagents (to **5**, **8-12**), and carbonyl derivatives (to **7**, **15-26**, **28-30**). It can also be phenylated with (benzene)(tricarbonyl)chromium (to **13**) and thiolated with diphenyl disulfide (**14**). The products arise from Re attack of the electrophiles on the enolate carbon, i.e., with relative topicity *lk*, as shown by chemical correlation in two cases (**4**, **6**) and by an X-ray crystal structure analysis of the benzaldehyde adduct (**7**). With the addition of the enolate **3** to aldehydes and to unsymmetrical ketones some Michael-additions (**24**, **26**, **27**) occur with high enantioface differentiation. Cleavage of the products from enolate **3** furnishes α-alkylated proline derivatives (**4**, **6**, **31**, **33-39**). The overall process is an electrophilic substitution of the α-proton of proline with retention of configuration at the asymmetric carbon atom. Since no external chiral auxiliary is necessary to achieve this transformation without loss of enantiomeric purity, it is called a self-reproduction of chirality (Scheme I).

Most amino acids are inexpensive and available in both enantiomeric forms. They can be valuable starting materials[5,6] for the synthesis of other enantiomerically pure products.[7,8] Thus, any new type of transformation of amino acids occurring without

(1) For a preliminary account, see: Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704.

(2) Following a different concept, an aspartate derivative was α-alkylated to give products of ca. 65% ee: Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971.

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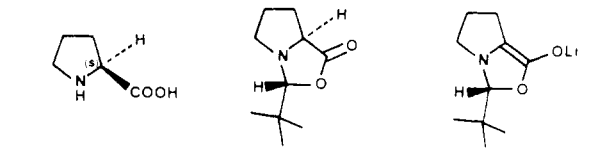
extensive loss of enantiomeric purity is bound to be synthetically useful.[9] The most intriguing problem appears to be their α-alkylation without racemization[10,11] and without use of an *external* chiral auxiliary.[12] If this could be achieved, a simple access would be opened not only to an increased number of nonracemic starting materials but also to the α-alkylated α-amino acids themselves, whose biological activity has been recognized only recently.[13]

As part of our project of generating chiral lithium enolates from α- and β-heterosubstituted carboxylic esters,[1,2,14-16] we also tried to prepare acetal-type derivatives of amino acids. The results obtained with proline are described herein.

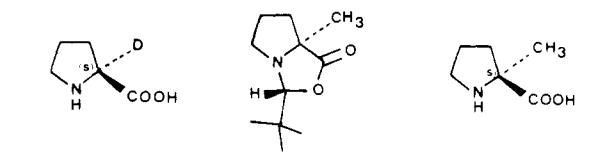
Generation of the (*R*)-Enolate 3 Derived from Proline and Configuration of Its Products with Electrophiles

Under acid catalysis and with azeotropic removal of water, proline (**1**) and excess pivalaldehyde condense[17] to give a single product **2**. The bicyclic compound **2** is extremely sensitive to hydrolysis which leads to proline of unchanged optical activity, proving that no racemization has occurred during the condensation. As shown previously,[17] **2** is also thermally labile, losing CO_2 above 100 °C in the reversal of a dipolar [3 + 2] cycloaddition.[18] Crystallization from pentane at −40 °C or Kugelrohr distillation at 5×10^{-2} torr furnishes the [3.3.0]-bicyclic N,O-acetal **2** in pure form for subsequent reactions.

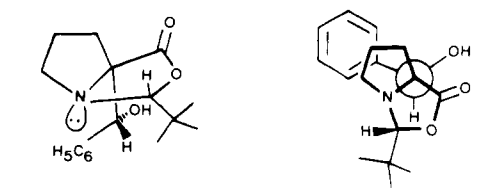
Deprotonation to the chiral lithium enolate **3** is carried out with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C. Deuterolysis of this enolate[19] furnishes α-deuterioproline (**4**) of the same sense of chirality, i.e., in this case of the same sense of rotation as the starting proline (**1**).



(−)-1 2 3

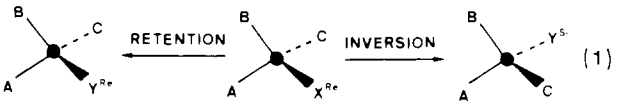


(−)-4 5 6



a 7 b

Methylation with iodomethane leads to a single diastereomer, **5**, which is much more stable than its precursor **2** toward both thermal decarboxylation and hydrolysis. In fact, it requires 8 h of stirring in 15% aqueous hydrobromic acid at room temperature to hydrolyze **5** to α-methylproline (**6**). This is isolated as the laevorotatory hydrobromide ($[\alpha]_D$ −28.6° (lit.[20] $[\alpha]_D$ −28.9°)) to which the (*S*) configuration has been previously assigned.[20]



(1)

(priority sequence A>B>C)

The configuration of a third product (**7**) was determined by crystal structure X-ray analysis (see the following section). This hydroxy derivative **7** was obtained from the enolate **3** and benzaldehyde in ca. 70% yield. Although three asymmetric carbon atoms are present in the adduct **7**, one stereoisomer is formed with very high diastereoselectivity (94% ds[1]).

The configuration of this product is as shown in the formulas **7a** and **7b** (see X-ray analysis, Figure 1).

The following conclusions and generalizations are possible from the assignments of configuration of the three products **4**, **6**, and **7** obtained from the enolate **3**.

(i) If we use the definition[21] indicated in eq 1, the three electrophilic substitutions occur with *retention* of configuration.

(3) Postdoctoral fellow (Bundesstipendiat), ETH Zürich, 1982.

(4) Part of the results described here will be the subject of the Ph.D. thesis of R.N.

(5) An example is the synthesis of cytochalasin: Stork, G.; Nakahara, Yo.; Nakahara, Yu.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7775. Pyne, S. G.; Hensel, M. J.; Byrn, S. R.; McKenzie, A. T., and Fuchs, P. L. *Ibid.* **1980**, *102*, 5960.

(6) Review: Kleeman, A. *Chem. Ztg.* **1982**, *106*, 151. Drauz, K.; Kleemann, A.; Martens, J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 584.

(7) "EPC (enantiomerically pure compounds) syntheses": Seebach, D.; Hungerbühler, E. In "Modern Synthetic Methods"; Scheffold, R., Ed.; Salle + Sauerländer: Aarau, 1980; Vol. 2, pp 91-171.

(8) Pool of chiral building blocks: Seebach, D.; Kalinowski, H.-O. *Nachr. Chem. Tech.* **1976**, *24*, 415.

(9) See the Friedel-Crafts-type acylations to give α-amino aryl ketones: Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157.

(10) Complete racemization takes place in the deprotonation of oxazolinones (azalactones) (Lohmar, R.; Steglich, W. *Chem. Ber.* **1980**, *113*, 3706). Also, the enolates of imine derivatives of amino acid esters give racemic alkylation products (Stork, G.; Leong, A. Y. W.; Touzin, A. M. *J. Org. Chem.* **1976**, *41*, 3491. Fitt, J. J.; Gschwend, H. W. *Ibid.* **1977**, *42*, 2639. Vevert, J.-P.; Dorsselaer, V. V.; Kolb, M. *Ibid.* **1979**, *44*, 2732). For the enantioselective protonation of lithium enolates from imino derivatives of amino acid esters with optically active carboxylic acids, see: Duhamel, C.; Plaquevent, J. Ch. *J. Am. Chem. Soc.* **1978**, *100*, 7415. Finally, α-alkylation of amino acids was also achieved through isonitrile derivatives, again with production of racemic materials: Schöllkopf, U.; Hoppe, D.; Jentsch, R. *Chem. Ber.* **1975**, *108*, 1580. For enolates of silyl esters of *N*,*N*-bis(trimethylsilyl)glycine, see: Rühlmann, K.; Kuhrt, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 809. Shanzer, A.; Somekh, L.; Butina, D. *J. Org. Chem.* **1979**, *44*, 3967.

(11) In view of the fact that (mixed) aggregates of lithium enolates may be the reactive species (Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. Seebach, D.; Amstutz, R.; Dunitz, J. D. *Ibid.* **1981**, *64*, 2622), occasional reports[2] (Braña, M. F.; Garrido, M.; Lopez, M. L.; Sanz, A. M. *J. Heterocycl. Chem.* **1980**, *17*, 829) about nonracemic products of alkylation appear to be less unbelievable.

(12) (a) Schöllkapf's method (Schöllkopf, U.; Neubauer, H. J. *Synthesis* **1982**, 861 and references cited therein) uses one amino acid for asymmetric induction of the α-alkylation of another amino acid. The method involves the preparation with the Meerwein salt of lactim ethers of diketopiperazines which are subsequently deprotonated on one of the two asymmetric centers. (b) The diketopiperazine of proline has been deprotonated to a chiral enolate which was ethylated and thiolated (Poisel, H.; Schmidt, U. *Chem. Ber.* **1972**, *105*, 625). In this case, a second proline moiety functions as the chiral auxiliary.

(13) The powerful reversible inhibition of amino acid decarboxylases by α-methyl analogues of some α-amino acids stimulated the search for convenient synthetic methods: "Amino acids, Peptides, and Proteins"; The Chemical Society: London, 1979; Vol. 10, p 11.

(14) Malic ester: Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197.

(15) β-Hydroxybutyric ester: Züger, M.; Weller, Th.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2005. Cf.: Fráter, G. *Ibid.* **1979**, *62*, 2825, 2829.

(16) Acetonide of tartaric esters: Naef, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1030.

(17) Compound **2** was previously obtained from the trimethylsilyl ester of *N*-trimethylsilylproline and pivalaldehyde: Eschenmoser, A. *Chem. Soc. Rev.* **1976**, *5*, 377.

(18) Review on 1.3-dipolar cycloadditions: Huisgen, R. *Angew. Chem.* **1963**, *75*, 604. Review on 1.3-dipolar cycloreversion: Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 721.

(19) As in many other deprotonations with LDA, simple deuterolysis and NMR analysis of the D-incorporation does not indicate the degree of enolate formation (**2** → **3**): even solutions which give 90% yield of products with other electrophiles do not lead to more than ca. 25% deuteration. Obviously, in the reaction [**3** + $HN(CHMe_2)_2$] + DOR → proline the NH proton is largely transferred to the enolate. Removal of this NH proton by addition of butyllithium prior to deuterolysis leads to highly labeled proline [**3** + LDA] + DOR → **4**.

(20) Ellington, J. J.; Honigberg, I. L. *J. Org. Chem.* **1974**, *39*, 104. Overberger, C. G.; Jon, Y. S. *J. Polym. Sci., Polym. Chem. Ed.* **1977**, *15*, 1413.

(21) Wintner, C. *J. Chem. Educ.*, in press.

(ii) The *tert*-butyl group in the bicyclic proline derivative **2** is on the exo face, in a cis relationship with the bridgehead hydrogen; therefore, **2** is the (2*R*,5*S*) enantiomer of the *u* diastereomer,[22] as indicated in the formula.

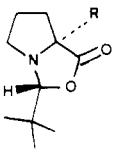
(iii) The enolate derived from (*S*)-proline has (*R*) chirality, see **3**.

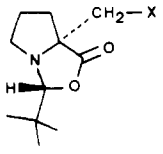
(iv) The nucleophilic center of **3** is attacked by all types of electrophiles from the Re face (*lk*-1.3-induction[22]). This puts both the *tert*-butyl group and the newly introduced substituent cis to each other, on the exo side of the 1-aza-3-oxabicyclo[3.3.0]octane system.

(v) The two trigonal centers of the enolate **3** and of benzaldehyde are joined with a relative topicity *ul* to give the adduct **7**. This is compatible with an O···Li···O chelated transition state,[23-25] with the larger phenyl group below the pyrrolidine ring and the smaller hydrogen atom near the *tert*-butyl group, see **7b**. We assume that the other diastereoselective additions of the enolate **3** to trigonal centers occur in an analogous fashion.

Reactions of the Enolate 3 with Various Electrophiles. Scope and Limitations

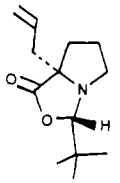
Alkylations and Heteroelectrophiles. With the more reactive alkylating reagents, such as iodomethane, allyl and benzyl bromide, *N*,*N*-dimethylmethyleneammonium chloride,[27] and α-halo acetic ester and amide the products **5** and **8–12** are formed in moderate to excellent yields and with essentially complete diastereoselection. The less reactive alkyl halides such as iodoethane and *sec*- and *tert*-butyl iodide give either no product or complex mixtures. In the case of allylation, the enantiomeric product **8′** derived from (*R*)-proline was also obtained. Phenylation with (benzene)(tricarbonyl)chromium[28] leads to **13** and thiolation[12b] with diphenyl disulfide produces **14**, both as single diastereomers.

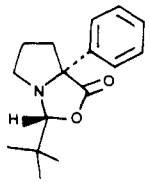


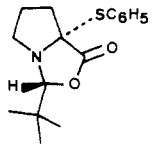


5 R=CH$_3$ (93%y)
8 R=CH$_2$-CH=CH$_2$ (87%y)
9 R=CH$_2$-C$_6$H$_5$ (91%y)

10 X=N(CH$_3$)$_2$ (56%y)
11 X=COOCH$_3$ (40%y)
12 X=CON(CH$_3$)$_2$ (70%y)

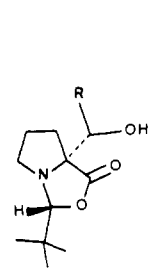


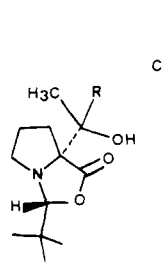


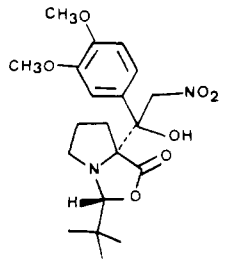


8′ 13 (30%y) 14 (84%y)

Additions to Carbonyl Groups of Aldehydes and Ketones. While addition to the symmetrical acetone gives a single diastereomer (**17**), aldehydes (to **7**, **15**, **16**) and unsymmetrical ketones (to **18–22**) give two isomers, epimeric at the carbinol center (see discussion above). One of these normally predominates to the extent of more than 70%, and sometimes up to 95%. The chemical yields are high even with highly acidic ketones such as acetoacetic ester (to **18**), a substituted ω-nitroacetophenone (to **19**), or tetralones (to **20–22**).



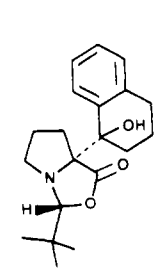


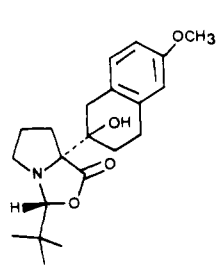


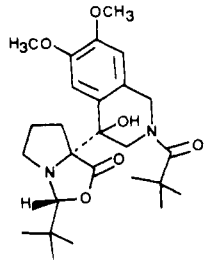
7 R=C$_6$H$_5$ (72%y,94%ds)
17 R=CH$_3$ (93%y)
19 (79%y,83%ds)

15 R=CH$_3$ (88%y,94%ds)
18 R=CH$_2$COOCH$_3$ (67%y,51%ds)

16 R=t-C$_4$H$_9$ (85%y,83%ds)







20 (70%y,73%ds) 21 (67%y,72%ds) 22 (91%y,>95%ds)

Michael Additions. There are only a few examples of highly diastereoselective intermolecular Michael additions (see the discussions in ref 25 and 29). When added to cyclohexenone in THF, enolate **3** gave a 5:2 mixture of two constitutional isomers, the 1.2-adduct **23** and the 1.4-adduct **24**, which could be separated and which are both ca. 95% configurationally pure. The cosolvents hexamethylphosphoric triamide (HMPT) or the urea **25**[30] almost totally suppress the Michael addition. The product **26** of conjugate addition is formed exclusively with *N*-benzyl-2-pyridone, while the nitroalkylation product **27** is formed with 85% diastereoselectivity.

Acylation of the enolate **3** was first observed when, in the addition to the ω-nitroacetophenone, the primary adduct (cf. **19**), a lithium alkoxide, underwent retro-nitroaldol cleavage to give the β-keto ester **29**. Acylation of **3** with acid chloride, anhydride, or ester produced the β-dicarbonyl derivatives **28–30**[10c] which were all rather unstable (see Experimental Section).

Cleavage of the N,O-Acetal Moiety of the Products from 3 and Electrophiles

The hydrolytic cleavage of the products from enolate **3** turns out to be most difficult. While the parent compound **2** becomes pale on contact with air because insoluble proline forms spontaneously, the methylation product **5** requires 15% aqueous HBr at room temperature (**6**, see above), and the benzylated derivative **9** requires 48% HBr at reflux temperature to give the amino acid **21**.[10b] Alkaline hydrolysis could not be effected, even under the most stringent conditions.[31] The reluctance to forming tetrahedral

(22) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.
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(24) Reviews about diastereoselective aldol additions: Heathcock, C. H. *Science* **1981**, *214*, 395. Evans, D. A.; Nelson, J. V.; Taber, T. R. "Topics in Stereochemistry"; John Wiley: New York, 1982; Vol. 13, pp 1–115.
(25) Seebach, D.; Goliński, *Helv. Chim. Acta* **1981**, *64*, 1413.
(26) Johnson, C. K. "Program ORTEP", Oak Ridge National Laboratory Report, 1965, ORNL-3794.
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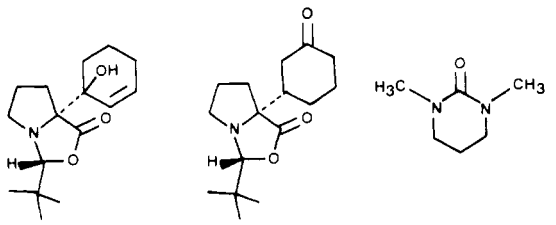
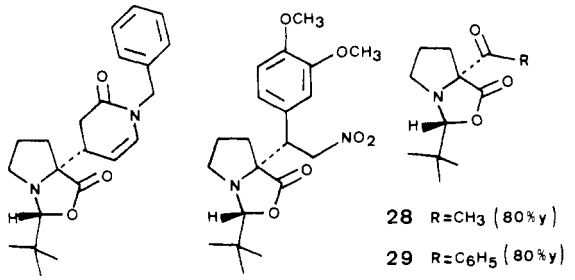
(28) Semmelhack, M. F.; Hall, H. T.; Yoshifuji, M.; Clark, G. *J. Am. Chem. Soc.* **1975**, *97*, 1247.
(29) Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1637. Seebach, D.; Blarer, S. J. *Chem. Ber.*, in print.
(30) The urea DMPU has properties as a cosolvent very similar to HMPT [Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705. Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 3851. Results of Ames tests show that DMPU does not exhibit genetic activity and is not mutagenic. In contrast, HMPT has been shown to be carcinogenic [International Agency for Research on Cancer Monographs, 1977, Vol. 15, p 211].

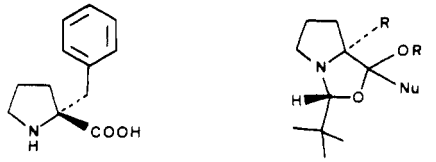


23 (50%y,95%ds) · 24 (21%y,95%ds) 25 (DMPU)

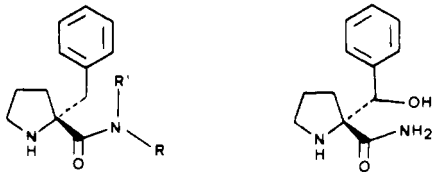


26 (50%y,>95%ds) 27 (40%y,85%ds) 28 R=CH_3 (80%y) 29 R=C_6H_5 (80%y) 30 R=OCH_3 (85%y)

intermediates **32** may have steric reasons (hexasubstituted ethane!); but it is also conceivable that stereoelectronic effects are responsible[32] for failure of the tetrahedral intermediate to undergo the desired bond cleavage. With lithium amides pivalaldehyde



31 32



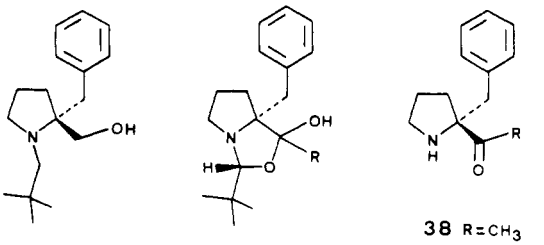
33 R=R'=CH_3
34 R=CH_3, R'=H 35

is removed to give[33] α-substituted proline amides, as demonstrated with the conversion of the products **7** and **9** to carboxamides **33–35**.

Other strongly nucleophilic reagents also lead to cleavage of the ring. Thus, lithium aluminum hydride furnishes the *N*-neopentyl-substituted amino alcohol **36**. Methyl- and phenyllithium add to give, after nonacidic aqueous workup, the quite stable isolable hemiacetals of type **37** which lose pivalaldehyde upon treatment with acid, or thermally during distillation, to give **38** or **39**.

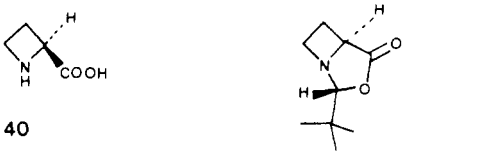
Products of Condensation between Other Amino Acids and Pivalaldehyde

Bicyclic compounds similar to **2** were also obtained from (*S*)-azetidinecarboxylic acid (**40** → **41**) and from the formaldehyde acetal of (*R*)-cystein[34] (**42** → **43**). The azaoxabicyclo[3.2.0]-heptane derivative **41** was, however, isolated as a racemate, the

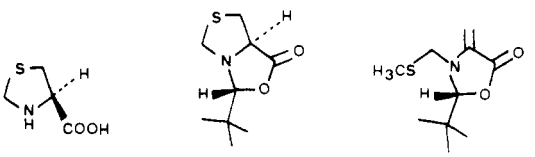


36 37 38 R=CH_3 39 R=C_6H_5

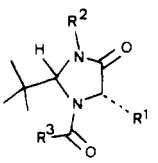
enolate of which could not be generated and alkylated in good yields. On the other hand, the cystein derivative **43** underwent β-elimination with LDA to give, after addition of iodomethane, the methyleneoxazolidinone **44** with the surprisingly high specific rotation of −277°. The exocyclic double bond of **44** has a so-called captodative substitution[35] and should be reactive toward radicals.[36] Neither the six-ring derivative pipecolic acid nor acyclic alkylamino acids could be condensed with pivalaldehyde, in spite of numerous attempts under a variety of conditions. Only recently did we discover that open-chain amino acids can be α-alkylated through enolates of the imidazolidinone **45**. A separate account of these results is in preparation.



40 41



42 43 44



45

Discussion of the Results

The α-alkylation of proline without racemization, as described herein, can be called a *self-reproduction of chirality*,[37] see Scheme I. The center of chirality of proline induces selective generation of a new center in step A. In step B, the original center is destroyed by deprotonation to give a chiral, nonracemic enolate. Attack at this enolate in step C is subject to asymmetric induction by the acetal center. After this diastereoselective reaction, the auxiliary center can be removed, step D, to give the product of overall substitution with retention of configuration.[12b]

The chiral enolate **3** has most unusual properties: (i) It adds to trigonal acceptor centers of the type present in (AB)C=X with excellent diastereoselectivity. (ii) This is true even if a hexasubstituted ethane bond is formed, as for instance with unsymmetrical ketones. (iii) The basicity of enolate **3** is surprisingly low. (iv) The nucleophilicity is only great with carbonyl substrates (**3** is a carbonylophile). Its nucleophilicity toward alkyl halides, its S_N reactivity, is poor. (v) Cosolvents which favor 1,4 addition

(31) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.
(32) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463. Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: Oxford, 1981.
(33) Yang, K.-W.; Cannon, J. G.; Rose, J. G. *Tetrahedron Lett.* **1970**, 1791.
(34) Schubert, M. P. *J. Biol. Chem.* **1936**, *114*, 341.
(35) Review: Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917.
(36) These reactions are pursued in our laboratory in an independent study.
(37) This principle can also be realized with other α-XH-substituted carboxylic acids, see ref 1 and Fráter et al.: Fráter, G.; Müller, V.; Günther, W. *Tetrahedron Lett.* **1981**, 4221.

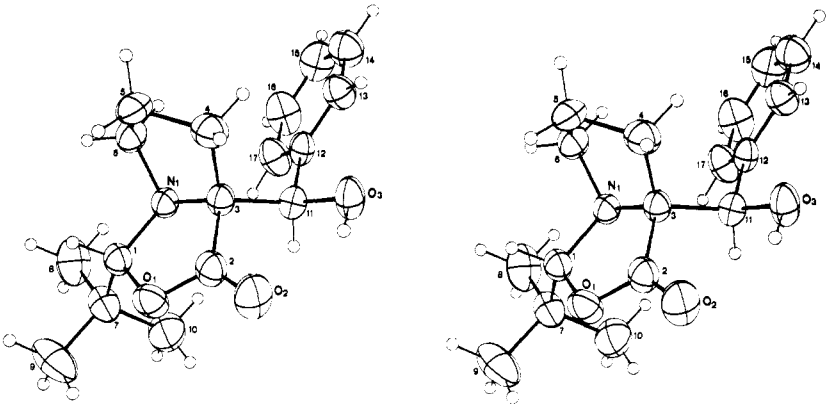
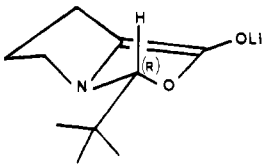


Figure 1. Stereoview of molecule **7**. Vibration ellipsoids for C, N, and O are drawn at the 50% probability level.[26] Details of the structure determination are available as supplementary material, in which the structure of **7** is also discussed.

of 2-lithio-1,3-dithiane nucleophiles[38] cause **3** to add almost exclusively in a 1,2 fashion to cyclohexenone.[39]

These properties must have structural reasons behind them. In fact, the enolate **3** has several unusual structural features, see formula **46**: Its double bond is also part of an enamine and of



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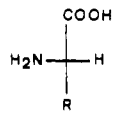
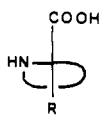


47

R	cf.
CH_3, alanine	5
$CH_2C_6H_5$, phenyl-alanine	9
CH_2COOH, aspartic acid	11, 12
$CH(OH)-CH_3$, threonine	16



48

an enol ether. Furthermore, the double bond is strained, with distortions of the normal 120° angles at the nucleophilic bridgehead center. Anomeric effects, aggregation, and/or unusual location of the lithium[11] are further possible reasons for the characteristic properties of this enolate. Its instability above ca. −30 °C has so far prevented isolation and crystal structure analysis.[11]

Better cleavage procedures for the products from **3** are under active investigation in our laboratories. They will eventually improve the access to the α-alkylated prolines, a type of unnatural amino acids which can also be thought of as amino acids which are α- and N-alkylated by a $(CH_2)_3$-link, cf. **47** with **48**.

Experimental Section

General Remarks. Melting points and boiling points are uncorrected. Reagents and solvents were purified in the usual way. All reactions involving lithium derivatives were carried out under anhydrous conditions in an Argon atmosphere. Spectra were recorded with the following instruments. IR: Perkin-Elmer Spectrophotometer 297. ^1H NMR: Varian-EM-390 (90 MHz) and Varian XL-100 (100 MHz). ^{13}C NMR: Varian-CFT-20 (20 MHz). Mass spectra: Hitachi Perkin-Elmer RMU-6M. IR data are presented in cm^{-1}. NMR spectra were (unless noted otherwise) recorded with $(CH_3)_4Si$ as internal standard. Optical rotations were determined with a Perkin-Elmer Model 241 polarimeter. Kugelrohr distillations were carried out on a Büchi-GKR-50 apparatus and reported boiling points correspond to air-bath temperatures. Routine analyses agree with calculated values within ±0.3%. The diastereomeric composition of crude products was determined by ^1H or ^{13}C NMR. Flash chromatography was performed according to the method described by Still et al.[40]

(2*R*,5*S*)-2-*tert*-Butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (2). To a suspension of 13.0 g (113 mmol) of (*S*)- or L-proline (**1**) in 400 mL of pentane was added 60 mL (560 mmol) of pivalaldehyde[41] and 0.2 mL of trifluoroacetic acid. The mixture was refluxed for 48 h with azeotropic removal of the water formed. The resulting clear solution was concentrated under reduced pressure. The residue was distilled in a Kugelrohr oven to afford 19.0 g (92%) of **2**. Alternatively, the crude product could be crystallized from pentane at −40 °C: bp 85 °C (0.05 mm); mp 20–25 °C; $[\alpha]^{25}_D$ −24.7° (*c* 2.4; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.51 (s, 1 H, H–C2), 3.80 (dd, J_1 = 6 Hz, J_2 = 6 Hz, 1 H, H–C5), 3.36–3.06 (m, 1 H, H–C8), 2.96–2.63 (m, 1 H, H–C8), 2.30–1.96 (m, 2 H, H_2C6), 1.93–1.60 (m, 2 H, H_2C7), 0.93 (s, 9 H, $(H_3C)_3C$–C2); ^{13}C NMR ($CDCl_3$) δ 177.76 (C 4), 108.04 (C 2), 62.84 (C 5), 58.93 (C 8), 37.49 (C–C2), 29.72, 25.18 (C6, C7), 24.21 ($(H_3C)_3C$).

(*S*)-(−)-α-Deuterioproline (4). A solution of 0.92 g (5 mmol) of **2** in THF (30 mL) was cooled to −78 °C in a dry ice–acetone bath and 5 mL of a 1 M THF solution of LDA (5 mmol) was added. After the mixture was stirred for 30 min, a hexane solution of butyllithium (3.2 mL, 5 mmol) was added and then the reaction mixture was stirred for 1 h. Quenching with 2 mL of 38% DCl/D_2O was followed by concentration under reduced pressure. The residue was subjected to cation exchange chromatography on 20 g of Dowex 50 W resin. Elution with 400 mL of 2 N ammonia and subsequent removal of water gave 0.46 g (79%) of **4** of $[\alpha]^{25}_D$ −67° (*c* 3.0; H_2O).

General Procedure for Reactions of the Enolate 3 with Various Electrophiles. Unless noted otherwise, 1.05 equiv of a 1 M LDA solution in THF/hexane 1:3 was added to a 0.17 M solution of **2** in THF at −78 °C. After 30 min, 1.10 equiv of the electrophile were added, and the temperature was allowed to warm to −30 °C over a period of 2 h. The resulting mixture was partitioned between dichloromethane and water. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. Specific details are given for each compound.

(2*R*,5*S*)-2-*tert*-Butyl-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (5). Methyl iodide (1.56 g, 11 mmol) and 1.83 g (10 mmol) of **2** were employed. Kugelrohr distillation afforded 1.83 g (93%) of **5** as a colorless oil: bp 85 °C (0.05 mm); $[\alpha]^{25}_D$ −29.8° (*c* 0.7; $CHCl_3$); IR ($CHCl_3$) 2950 (m), 2860 (w), 1760 (s); ^1H NMR ($CDCl_3$) δ 4.24 (s, 1 H, H–C2), 3.26–2.66 (m, 2 H, H_2C8), 2.24–1.50 (m, 4 H, H_2C6, H_2C7), 1.36 (s, 3 H, H_3C–C5), 0.88 (s, 9 H, $(H_3C)_3C$–C2); ^{13}C NMR ($CDCl_3$) δ 178.39 (C4), 105.53 (C2), 68.72 (C5), 57.79 (C8), 38.64 (H_3C–C5), 36.35 (C–C2), 25.45, 25.33 (C6, C7), 24.09 ($(H_3C)_3C$); MS 197 (M^+, 1.2), 154 (4), 140 (17), 112 (100), 96 (13). Anal. Calcd for $C_{11}H_{19}NO_2$ (197.28): C, 66.97; H, 9.71; N, 7.16. Found: C, 67.07; H, 9.87; N, 7.16.

(*S*)-2-Methylproline Hydrobromide (6). To a solution of 10 mL of 15% aqueous HBr was added 0.50 g (2.5 mmol) of **5** and the mixture was stirred for 8 h at room temperature. Concentration under reduced pressure gave a solid which was repeatedly triturated with dry ether to remove soluble material. Colorless crystals of (**6**) (0.44 g, 80%) were

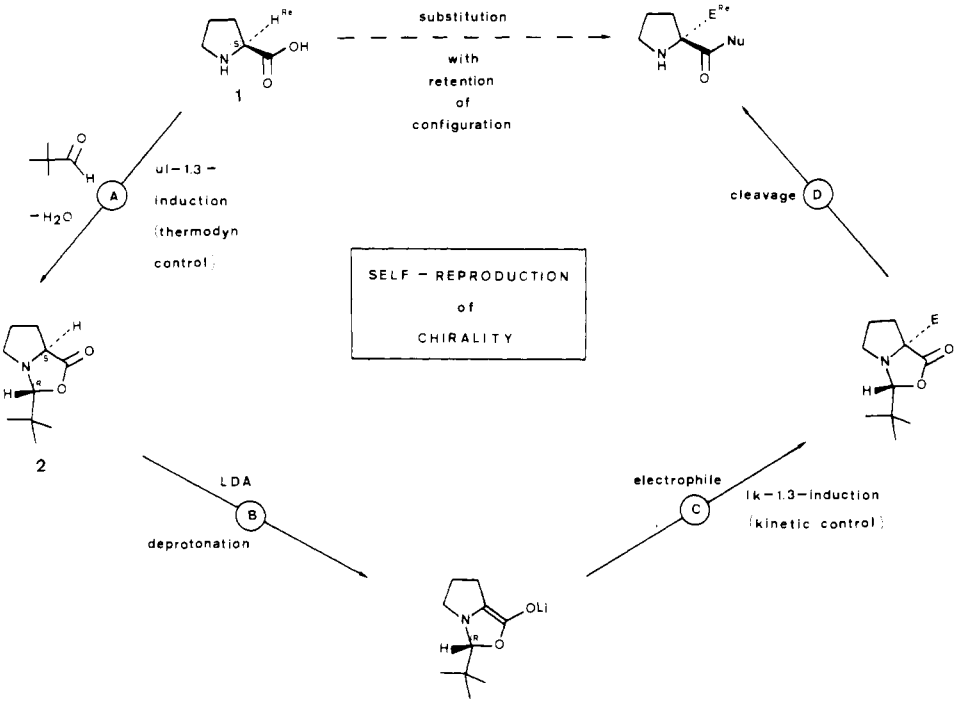
(38) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385. Brown, C. A.; Yamaidi, A. *J. Chem. Soc., Chem. Commun.* **1979**, 100. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239 and references cited therein.

(39) For similar results with lithiated nitriles see: Hünig, S.; Wehner, G. *Chem. Ber.* **1980**, *113*, 302.

(40) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(41) To prevent partial racemization an excess of pivalaldehyde is necessary.

Scheme I



obtained: mp 135 °C (lit.[20] mp 136–137 °C); $[\alpha]^{20}_D$ −28.6° (*c* 1.0; CH_3OH) (lit.[20] $[\alpha]^{20}_D$ −28.9° (*c* 1.0; CH_3OH)); ^1H NMR (D_2O, HDO ≡ 4.70 ppm) 3.36 (t, *J* = 7 Hz, 2 H, H_2C5), 2.45–1.80 (m, 4 H, H_2C3, H_2C4), 1.60 (s, 3 H, H_3C).

(2*R*,5*R*,1′*R*)-2-*tert*-Butyl-5-(1′-hydroxybenzyl)-1-aza-3-oxabicyclo-[3.3.0]octan-4-one (7). From benzaldehyde (1.16 g, 11 mmol) and 1.83 g (10 mmol) of **2** were obtained 2.09 g (73%) of **7** as colorless crystals (from ether/pentane). Diastereomeric ratio in the crude product 95:5; mp 110 °C (mp of the racemate 106 °C, see discussion of the X-ray crystal structure determination); $[\alpha]^{25}_D$ +3.9° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3520 (br, m), 2960 (m), 2870 (m), 1750 (s); ^1H NMR ($CDCl_3$) δ 7.70–7.20 (m, 5 H, arom.), 5.00 (s, 1 H, H–C1′), 4.30 (s, 1 H, H–C2), 4.03 (s, 1 H, OH), 2.74–2.42 (m, 2 H, H_2C8), 2.30–1.90 (m, 4 H, H_2C7, H_2C6), 1.00 (s, 9 H, $(H_3C)_3$ C–C2); ^{13}C NMR ($CDCl_3$) 179.50 (C 4), 138.04, 127.77, 127.67 (arom C), 105.79, 104.69 (C2), 75.19 (C1′), 74.13 (C5), 57.66, 57.03 (C8), 36.83 (C–C2), 33.05, 30.54, (C6), 24.55, 24.37 ($(H_3C)_3C$), 24.03 (C7); MS 290 (M^+ − 1, 0.7), 274 (0.7), 204 (3), 183 (93), 182 (100). Anal. Calcd for $C_{17}H_{23}NO_3$ (289.38): C, 70.56; H, 8.01; N, 4.84. Found: C, 70.51; H, 7.97; N, 4.91.

(2*R*,5*R*)-5-Allyl-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (8). Allyl bromide (1.33 g, 11 mmol) and 1.83 g (10 mmol) of **2** gave after Kugelrohr distillation product **8** (1.94 g, 87%) as a yellow resin: bp 80 °C (0.01 mm); $[\alpha]^{24}_D$ +13.8° (*c* 0.8; $CHCl_3$); IR ($CHCl_3$) 2950 (m), 2870 (m), 1758 (s); ^1H NMR ($CDCl_3$) δ 6.13–5.60 and 5.23–4.93 (m, 3 H, olefin), 4.20 (s, 1 H, H–C2), 3.06–2.70 (m, 2 H, H_2C8), 2.34 (d, *J* = 7 Hz, 2 H, H_2C1'), 2.13–1.33 (m, 4 H, H_2C7 and H_2C6), 0.87 (s, 9 H, $(H_3C)_3C$–C2); ^{13}C NMR ($CDCl_3$) δ 178.00 (C4), 132.94 (C2), 118.98 (C3′), 105.48 (C2′), 71.45 (C5), 57.93 (C8), 42.04 (C6), 36.40 ($(H_3C)_3C$), 35.28 (C1′), 24.91 (C7), 24.25 ($(H_3C)_3C$); MS 222 (M^+ − 1, 0.8), 138 (100), 110 (32), 96 (35), 41 (27). Anal. Calcd for $C_{13}H_{21}NO_2$ (223.32): C, 69.92; H, 9.48; N, 6.27. Found: C, 69.77; H, 9.56; N, 6.13.

(2*S*,5*S*)-5-Allyl-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (8′). All spectroscopic data were identical with those of the (+)-enantiomer **8**. $[\alpha]^{25}_D$ −13.1° (*c* 1.8; $CHCl_3$). Anal. Calcd for $C_{13}H_{21}NO_2$ (223.32): C, 69.92; H, 9.48; N, 6.27. Found: C, 70.11; H, 9.49; N, 6.22.

(2*R*,5*R*)-5-Benzyl-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (9). Benzyl bromide (1.88 g, 11 mmol) and 1.83 g (10 mmol) of **2** afforded after Kugelrohr distillation 2.48 g (91%) of **9** as colorless crystals: mp 66 °C; bp 150 °C (0.3 mm); $[\alpha]^{25}_D$ +16.1° (*c* 1.3; $CHCl_3$); IR ($CHCl_3$) 2950 (m), 2860 (m), 1765 (s); ^1H NMR ($CDCl_3$) δ 7.30 (br s, 5 H, arom), 4.24 (s, 1 H, H–C2), 3.10 (d, *J* = 13 Hz, 1 H, benzylic), 2.83 (d, *J* = 13 Hz, 1 H, benzylic), 2.76–2.53 (m, 2 H, H_2C8), 2.20–1.80 (m, 2 H, H_2C6), 1.64–1.28 (m, 2 H, H_2C7), 0.90 (s, 9 H, $(H_3C)_3C$–C2); MS 258 (M^+ − 15, 0.7), 230 (2), 229 (5), 188 (45), 182 (100). Anal. Calcd for $C_{17}H_{23}NO_2$ (273.38): C, 74.69; H, 8.48; N, 5.12. Found: C, 75.04; H, 8.47; N, 5.18.

(2*R*,5*R*)-2-*tert*-Butyl-5-(*N*,*N*-dimethylaminomethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (10). A cold solution of the enolate **3** (10 mmol), prepared according to the general procedure, was added to a suspension of 1.50 g (16 mmol) of *N*,*N*-dimethylmethylenimmonium chloride in 20 mL of THF at −78 °C.[42] After workup, Kugelrohr distillation afforded 1.34 g (56%) of **10** as a yellow resin: bp 90 °C (0.05 mm); $[\alpha]^{25}_D$ −45.2° (*c* 0.8; $CHCl_3$); IR ($CHCl_3$) 2950 (s), 2860 (m), 2815 (m), 2770 (m), 1770 (s); ^1H NMR ($CDCl_3$) δ 4.24 (s, 1 H, H–C2), 3.23–2.76 (m, 2 H, H_2C8), 2.53 (s, 2 H, H_2C–C5), 2.36 (s, 6 H, 2 H_3C–N), 2.30–1.46 (m, 4 H, H_2C6, H_2C7), 0.93 (s, 9 H, $(H_3C)_3C$–C2); MS 240 (M^+, 1), 139 (2), 96 (4), 58 (100). Anal. Calcd for $C_{13}H_{24}N_2O_2$ (240.35): C, 64.97; H, 10.06; N, 11.65. Found: C, 65.02; H, 10.14; N, 11.56.

(2*R*,5*R*)-2-*tert*-Butyl-5-(carbomethoxymethyl)-1-aza-3-oxabicyclo-[3.3.0]octan-4-one (11). Methyl α-bromoacetate (0.84 g, 5.5 mmol) and 0.91 g (5.0 mmol) of **2** yielded 0.51 g (40%) of distilled **11** as a colorless oil: bp 170 °C (0.05 mm); $[\alpha]^{25}D$ +5.40 (*c* 18.0, $CHCl_3$); IR ($CHCl_3$) 2460 (s), 2380 (m), 1770 (s), 1735 (s); ^1H NMR ($CDCl_3$) δ 4.17 (s, 1 H, H–C2), 3.60 (s, 3 H, OCH_3), 3.21–2.65 (m, 2 H, H_2C8), 2.65 (s, 2 H, benzyl), 2.33–1.41 (m, 4 H, H_2C6, H_2C7), 0.90 (s, 9 H, $(H_3C)_3C$–C2); MS 240 (M^+ − 15, 0.9), 224 (2.3), 198 (8.6), 170 (14.1), 142 (100). Anal. Calcd for $C_{13}H_{21}NO_4$ (255.30): C, 61.16; H, 8.29; N, 5.49. Found: C, 61.30; H, 8.57; N, 6.16.

(2*R*,5*R*)-2-*tert*-Butyl-5-((dimethylcarbamoyl)methyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (12). *N*,*N*-Dimethylchloroacetamide (0.67 g, 5.5 mmol) was used to alkylate 0.91 g (5.0 mmol) of **2**. Kugelrohr distillation gave 0.94 g (70%) of **12** as colorless crystals which were recrystallized from methanol: mp 92–93 °C; bp 170 °C (0.05 mm); $[\alpha]^{25}_D$ −1.9° (*c* 3.3; $CHCl_3$); IR ($CHCl_3$) 2960 (m), 2870 (m), 1770 (s), 1640 (s); ^1H NMR ($CDCl_3$) δ 4.23 (s, 1 H, H–C2), 3.40–2.86 (m, 2 H, H_2C8), 3.01 (s, 3 H, N–CH_3), 2.93 (s, 3 H, NCH_3), 2.86–2.66 (dublettsides m, 2 H, H–C1′), 2.60–1.50 (m, 4 H, H_2C6, H_2C7), 0.91 (s, 9 H, $(H_3C)_3C$–C2); MS 268 (M^+, 5.2), 253 (1.1), 211 (44.9), 180 (100), 155 (97). Anal. Calcd for $C_{14}H_{24}N_2O_3$ (268.35): C, 62.66; H, 9.01; N, 10.44. Found: C, 62.80; H, 9.02; N, 10.33.

(2*R*,5*R*)-2-*tert*-Butyl-5-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (13). A solution of 0.92 g (5 mmol) of **2** in THF (30 mL) was cooled to −78 °C and 5 mL of a 1 M THF solution of LDA (5 mmol) was added. After the mixture was stirred for 30 min, a solution of 1.2 g (5.5 mmol) of (benzene)(tricarbonyl)chromium in 10 mL of THF was added, and the temperature was allowed to warm to −30 °C over a period of 2 h. After cooling the mixture again to −78 °C, a solution of iodine (6 g, 23.7 mmol) was added rapidly and the resulting mixture was warmed to 20–25 °C for 3 h. The crude mixture was diluted with ether (equal

(42) Seebach, D.; Weller, T.; Protschuk, G.; Beck, A. K.; Hoekstra, M. S. *Helv. Chim. Acta* **1981**, *64*, 716.

volume) and washed sequentially with a 10-mL portion of saturated aqueous sodium bisulfite solution. The ether layer was dried and the solvent was removed under reduced pressure. Flash chromatography of the crude product with ethyl acetate/pentane (2:8, R_f 0.65) and subsequent Kugelrohr distillation gave 0.38 g (30%) of **13**: bp 110 °C (0.01 mm); $[\alpha]^{25}_D$ −3.2° (*c* 4.6, $CHCl_3$); IR (film) 3060 (w), 3030 (w), 2970 (s), 2880 (s), 1780 (s); ^1H NMR ($CDCl_3$) 7.76 (m, 2 H, arom), 7.30 (m, 3 H, arom), 4.45 (s, 1 H, H–C2), 3.46–2.86 (m, 2 H, H_2–C8), 2.58–1.56 (m, 4 H, H_2C6, H_2C7), 0.86 (s, 9 H, $(H_3C)_3C$–C2); MS 244 (M^+ − 15, 0.7), 216 (1.6), 215 (1.3), 203 (4.1), 174 (100). Anal. Calcd for $C_{16}H_{21}NO_2$ (259.33): C, 74.10; H, 8.16; N, 5.40. Found: C, 73.94; H, 8.15; N, 5.31.

(2*R*,5*R*)-2-*tert*-Butyl-5-(phenylthio)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (14). To a cold solution of the enolate **3** (5 mmol) prepared according to the general procedure was added 1.2 g (5.5 mmol) of diphenyl disulfide in 10 mL of THF. The crude product was subjected to flash chromatography with pentane/ethyl acetate (9:1, R_f 0.35) to afford 1.22 g (84%) of **14** as a yellow oil: $[\alpha]^{25}_D$ −4.3° (*c* 3.5, $CHCl_3$); IR ($CHCl_3$) 2970 (m), 2880 (m), 1780 (s); ^1H NMR ($CDCl_3$) δ 7.71 (m, 2 H, arom), 7.35 (m, 3 H, arom), 4.28 (s, 1 H, H–C2), 3.36–2.61 (m, 2 H, H_2C8), 2.23–1.50 (m, 4 H, H_2C6, H_2C7), 0.81 (s, 9 H, $(H_3C)_3C$–C2); MS 248 (M^+ − 43, 0.9), 247 (3.6), 218 (42.7), 190 (30.5), 110 (100). Anal. Calcd for $C_{16}H_{21}NO_2S$ (291.4): C, 65.95; H, 7.25; N, 4.81; S, 11.00. Found: C, 66.05; H, 7.41; N, 4.74; S, 10.98.

(2*R*,5*R*)-2-*tert*-Butyl-5-(1′-hydroxyethyl)-1-aza-3-oxabicyclo[3.3.0]-octan-4-one (15). Acetaldehyde (0.48 g, 11 mmol) and 1.83 g (10 mmol) of **2** were used to give Kulgerohr distilled **15** (2.0 g, 88%) as a colorless liquid: diastereomeric ratio 94:6; bp 110 °C (0.05 mm); $[\alpha]^{25}_D$ −6.3° (*c* 2.1; $CHCl_3$); IR ($CHCl_3$) 3540 (m), 2975 (m), 2870 (m), 1750 (s); ^1H NMR ($CDCl_3$) δ 4.50, 4.15 (s, 1 H, H–C2), 3.84 (q, *J* = 7 Hz, 1 H, H–C1′), 3.06–2.73 (m, 3 H, H_2C8), 2.26–1.43 (m, 4 H, H_2C7, H_2C6), 1.11 (d, 3 H, H_3C2'), 0.93 (s, 9 H, $(H_3C)_3C$–C2); MS 212 (M^+ − 15, 2), 183 (52), 182 (85), 168 (52), 96 (100). Anal. Calcd for $C_{12}H_{21}NO_3$ (227.31): C, 63.41; H, 9.31; N, 6.16. Found: C, 63.44; H, 9.28; N, 6.16.

(2*R*,5*R*)-2-*tert*-Butyl-5-(1′-hydroxy-2′,2′-dimethylpropyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (16). Pivalaldehyde (0.95 g, 11 mmol) and 1.83 g (10 mmol) of **2** were employed to give crude product which was subjected to flash chromatography with ether/hexane (10:1, R_f 0.35): 2.29 g (85%) **16**, colorless oil, diastereomeric ratio 6:4; $[\alpha]^{25}_D$ +8.9° (*c* 1.2; $CHCl_3$); IR ($CHCl_3$) 3500 (br m), 2960 (s), 2900 (m), 2870 (m), 1775 (s), 1755 (s); ^1H NMR ($CDCl_3$) δ 4.20, *4.17* (s, 1 H, H–C2), 3.73 (br s, 1 H, OH), 3.36, *3.24* (s, 1 H, H–C1′), 3.13–2.73 (m, 2 H, H_2C8), 2.57–1.97 (m, 2 H, H_2C6), 1.93–1.40 (m, 2 H, H_2C7), 1.06, *1.03*, and 0.93 (s, 18 H, 2 $(H_3C)C$); ^{13}C NMR ($CDCl_3$) δ *178.14*, 176.55 (C4), *103.79*, 103.37 (C2), *80.72*, 79.72 (C1′), *76.10*, 76.04 (C5), 55.90 (C8), *36.38*, 36.15, 36.04 (C–C2, C–C1′), 33.95, 32.74 (C6), *27.73*, 27.58 ($(H_3C)_3C$–Cl′), *24.76*, 24.61 ($(H_3C)_3C$–C_2), *24.32*, 24.06 (C7); MS 270 (M^+ + 1, 1.1) 183 (70), 182 (100), 168 (75), 96 (63). Anal. Calcd for $C_{15}H_{27}NO_3$ (269.39): C, 66.88; H, 10.10; N, 5.20. Found: C, 66.97; H, 10.17; N, 5.22.

(2*R*,5*R*)-2-*tert*-Butyl-5-(1′-hydroxy-1′-methylethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (17). From 0.64 g of acetone (11 mmol) and 1.83 g (10 mmol) of **2** a 94% yield of **17** (2.24 g) was obtained after Kugelrohr distillation. The tertiary alcohol is a colorless liquid of bp 95 °C (0.2 mm); $[\alpha]^{24}_D$ +3.4° (*c* 1.00; $CHCl_3$); IR ($CHCl_3$) 3520 (br w), 2960 (s), 2870 (w), 1760 (s); ^1H NMR ($CDCl_3$) δ 4.10 (s, 1 H, H–C2), 2.98–2.82 (m, 2 H, H_2C8), 2.56 (br s, 1 H, OH), 2.26–2.04 (m, 2 H, H_2C6), 1.92–1.68 (m, 2 H, H_2C7), 1.29 (s, 6 H, $(H_3C)_2C1'$), 0.96 (s, 9 H, $(H_3C)_3C$); MS 226 (M^+ − 15, 5), 184 (16), 183 (50), 182 (26), 168 (100). Anal. Calcd for $C_{13}H_{23}NO_3$ (241.33): C, 64.70; H, 9.61; N, 5.80. Found: C, 64.54; H, 9.45; N, 5.80.

(2*R*,5*R*)-2-*tert*-Butyl-5-(1′-hydroxy-1′-methyl-2′-(methoxycarbonyl)ethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (18). Methyl acetoacetate (0.58 g, 5 mmol) and the enolate of **2** (0.92 g, 5 mmol) were combined at −78 °C; 10 min after the addition of the electrophile the mixture was quenched with 0.5 mL of acetic acid. After the usual workup and Kugelrohr distillation 1.0 g (62%) of **18** was obtained as a pale yellow oil: ratio of diastereomers 2:1; bp 190 °C (0.01 mm); $[\alpha]^{25}_D$ −2.55 (*c* 7.5; $CHCl_3$); IR (film) 3520 (m, OH), 2980 (s), 2880 (m), 1770 (s), 1730 (s); ^1H NMR ($CDCl_3$) δ 4.11 (s, 1 H, H–C2), 3.71 (s, 3 H, OCH_3), 3.03–2.80 (m, 2 H, H_2C8), 2.66 (d, *J* = 9 Hz, H–C2′), 2.45 (s, H_2C2'), 2.20 (d, *J* = 9 Hz, H–C2′, 2 H), 2.18–1.93 (m, 2 H, H_2C6), 1.93–1.55 (m, 2 H, H_2C7), 0.97 (s, 9 H, $(H_3C)_3C$–C2); MS 300 (M^+ + 1, 0.6), 183 (70.8), 168 (100), 140 (48.3), 138 (56.3). Anal. Calcd for $C_{15}H_{25}NO_5$ (299.3): C, 60.18; H, 8.42; N, 4.68. Found: C, 60.25; H, 8.45; N, 4.66.

(2*R*,5*R*)-2-*tert*-Butyl-5-(1′-hydroxy-2′-nitro-1′-(3,4-dimethoxyphenyl)ethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (19). To a −78 °C solution of 0.92 g (5 mmol) of **2** in THF (30 mL) are added 5 mL of a 1 M THF/hexane solution of LDA (5 mmol). After the mixture was stirred for 30 min, 1.23 g (5.5 mmol) of ω-nitroacetoveratrone[43] (in 20 mL of THF) was added. Five minutes later, the reaction was quenched by addition of 0.5 mL of acetic acid. (Quenching after warming to room temperature gave only the elimination product **29**.) The usual workup procedure led to the isolation of **19** as colorless crystals (1.6 g, 79%): mp 136–138 °C; $[\alpha]^{25}_D$ +41.3° (*c* 1.5; $CHCl_3$); IR ($CHCl_3$) 3540 (w), 2970 (m), 2940 (w), 2910 (w), 2880 (w), 2840 (w), 1760 (s); ^1H NMR ($CDCl_3$) δ 7.26–6.78 (m, 3 H, arom), 5.56 (d, *J* = 12 Hz, 1 H, H–C2′), 4.76 (d, *J* = 12 Hz, 1 H, H–C2′), 4.46 (s, 1 H, OH), 4.13 (s, 1 H, H–C2), 3.87 (s, 6 H, OCH_3), 2.85–2.30 (m, 2 H, H_2C8), 2.23–1.18 (m, 4 H, H_2C6, H_2C7), 0.88 (s, 9 H, $(H_3C)_3C$–C2); MS 303 (M^+ − 105, 12.1), 247 (17.0), 246 (100), 231 (2.8), 230 (4.2). Anal. Calcd for $C_{20}H_{28}N_2O_7$ (408.4): C, 58.80; H, 7.15; N, 6.86. Found: C, 58.67; H, 7.01; N, 6.77.

(2*R*,5*R*)-2-*tert*-Butyl-5-(1′-hydroxy-1′,2′,3′,4′-tetrahydro-1′-naphthyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (20). α-Tetralone (1.61 g, 11 mmol) and 1.83 g (10 mmol) of **2** were employed. Flash chromatography with ether (R_f 0.55) gave 2.31 g (70%) of **20** as a yellow resin: diastereomeric ratio 7:3; $[\alpha]^{25}_D$ +8.7° (*c* 2.30; $CHCl_3$); IR ($CHCl_3$) 3590 (w), 3500 (br m), 2950 (s), 2865 (w), 1770 (s); ^1H NMR ($CDCl_3$) δ 8.25–8.05 and 7.35–7.01 (m, 4 H, arom), 4.13 (s, 1 H, H–C2), 3.63 (br s, 1 H, OH), 3.10–1.17 (m, 12 H, H_2C6), *1.05* and 1.00 (s, 9 H, $(H_3C)_3C$–C2); MS 330 (M^+ + 1, 0.6), 198 (3), 183 (100), 168 (96), 146 (32). Anal. Calcd for $C_{20}H_{27}NO_3$ (329.44): C, 72.92; H, 8.26; N, 4.25. Found: C, 73.11; H, 8.23; N, 4.18.

(2*R*,5*R*)-2-*tert*-Butyl-5-(2′-hydroxy-6′-methoxy-1′,2′,3′,4′-tetrahydro-2′-naphthyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (21). 6-Methoxy-2-tetralone (0.97 g, 5.5 mmol) and 0.91 g (5 mmol) of **2** gave after crystallization from methanol 1.2 g (67%) of **21**: diastereomeric ratio 7:3; mp 136–146 °C; $[\alpha]^{25}_D$ −42.4° (*c* 6.6; $CHCl_3$) (measured of the 7:3 mixture); IR ($CHCl_3$) 3540 (w, OH), 2965 (s), 2880 (m), 1765 (s); ^1H NMR ($CDCl_3$) δ 6.98 (dublettoides m, *J* = 9 Hz, 1 H, H–C7′), 6.75–6.61 (m, 2 H, H–C8′, H–C5′), 4.15 (s, 1 H, H–C2), 3.73 (s, 3 H, OCH_3), 3.20–2.66 (m, 6 H, H_2C1', H_2C4', H_2C8), 2.66–1.53 (m, 7 H, OH, H_2C3', H_2C6, H_2C7), 0.98 (s, 9 H, $(H_3C)_3C$–C2); ^{13}C NMR ($CDCl_3$) δ 176.82, 176.60 (C4), 157.69, 136.89, *136.70*, 130.41, 125.90, 112.98, 112.25 (arom C), 102.82, *102.62* (C2), 79.33, *79.05* (C2′), 75.52 (C5), 56.93, *56.57* (C8), 55.12, (OCH_3), 36.27 (C–C2), *35.73*, 35.29 (C1′), 32.41, *32.08* (C6), 28.99, *27.47* (C4′), 25.67, *25.49* (C3′), 24.99 $(CH_3)_3C$); MS 360 (M^+ + 1, 1.0), 183 (100), 168 (84.5), 138 (56.5), 126 (36.2). Anal. Calcd for $C_{21}H_{29}NO_4$ (359.44): C, 70.17; H, 8.13; N, 3.90. Found: C, 70.01; H, 8.01; N, 4.08.

(2*R*,5*R*)-2-*tert*-Butyl-5-(4′-hydroxy-6′,7′-dimethoxy-2′-pivaloyl-1′,2′,3′,4′-tetrahydroisochinolyl-4′)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (22). 6,7-Dimethoxy-2-pivaloyl-1,2,3,4-tetrahydroisochinolinone (1.6 g, 5.5 mmol) and 0.91 g (5 mmol) of **2** furnished a quantitative yield of crude **22** which was recrystallized from methanol: 2.15 g (91%) of **22**; mp 172–174 °C; $[\alpha]^{25}_D$ +49.12° (*c* 4.6; $CHCl_3$); IR ($CHCl_3$) 3440 (w), 3100 (w), 2960 (s), 2870 (m), 1770 (s), 1610 (s); ^1H NMR ($CDCl_3$) δ 8.41 (s, 1 H, H–C5′), 6.52 (s, 1 H, H–C8′), 5.10–4.76 (m, 2 H, H_2C1'), 4.60–4.26 (m, 2 H, H_2C3'), 4.17 (s, 1 H, H–C2), 3.96 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.03–2.73 (m, 2 H, H_2C8), 2.23–1.18 (m, 4 H, H_2C6, H_2C7), 1.29 (s, 9 H, $(H_3C)_3C$–CON), 1.06 (s, 9 H, $(H_3C)_3C$–C2); MS 292 (M^+ − 82, 17), 291 (16.4), 206 (66.2), 150 (10.5), 149 (11.0). Anal. Calcd for $C_{26}H_{28}N_2O_6$ (474.58): C, 65.80; H, 8.07; N, 5.90. Found: C, 65.31; H, 7.81; N, 5.95.

(2*R*,5*R*)-2-*tert*-Butyl-5-(1′-hydroxy-2′-cyclohexenyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (23) and (2*R*,5*R*)-2-*tert*-Butyl-5-(3′-oxocyclohexyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (24) from the Enolate 3 and Cyclohexenone. To a solution of the enolate **3** (5 mmol), prepared according to the general procedure, was added 2.4 mL of DMPU (**25**) at −78 °C. The mixture was stirred at −78 °C for 45 min, followed by addition of 0.53 g (5.5 mmol) of 2-cyclohexen-1-one. After the usual workup and flash chromatography with ether/pentane (1:1, R_f 0.42), 1.18 g (85%) of **23** was isolated as a colorless oil containing only traces of **24**.

In the absence of the cosolvent DMPU, 2-cyclohexen-1-one (0.53 g, 5.5 mmol) and enolate from 0.92 g (10 mmol) of **2** were allowed to react according to the general procedure. Flash chromatography with ether/pentane (1:1, R_f 0.8) gave 0.70 g (50%) of **23** as a colorless oil and 0.28 g (20%) of **24** as a byproduct.

Analytical data of **23**: bp 200 °C (0.01 mm); $[\alpha]^{25}_D$ −95.19° (*c* 2.29; $CHCl_3$); IR (film) 3530 (w), 2960 (m), 2870 (m), 1780 (s); ^1H NMR ($CDCl_3$) δ 6.00 (m, 1 H, H–C3′), 5.66 (m, 1 H, H–C2′), 4.11 (s, 1 H, H–C2), 3.00–2.81 (m, 2 H, H_2C8), 2.43 (s, 1 H, OH), 2.23–1.38 (m, 4 H, H_2C6, H_2C7), 0.98 (s, 9 H, $(H_3C)_3C$–C2); ^{13}C NMR ($CDCl_3$) δ 176.03 (C4), 133.59, 128.50 (C2′, C3′), 103.21 (C2), 79.53 (C1′), 73.81 (C5), 57.32 (C8), 36.33 (C–C2), 33.92 (C6′), 30.18, 25.19 (C6, C7), 25.02 ($(CH_3)_3C$), 24.21, 18.20 (C4′, C5′); MS 262 (M^+ − 17, 1.3), 183

(43) Lehr, F.; Gonnermann, J.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 2258.

(67.8), 182 (66.6), 168 (88.0), 138 (53.9). Anal. Calcd for $C_{16}H_{25}NO_3$ (279.3): C, 68.79; H, 9.02; N, 5.01. Found: C, 68.69; H, 8.87; N, 4.94.

Analytical data of **24**: bp 190 °C (0.01 mm); $[\alpha]^{25}_D$ −10.63 (*c* 1.4; $CHCl_3$); IR (film) 2960 (s), 2880 (s), 1770 (s), 1710 (s); ^1H NMR ($CDCl_3$) δ 4.20 (s, 1 H, H–C2), 3.01–2.76 (m, 2 H, H_2C8), 2.66–1.26 (m, 13 H, H_2C6, H_2C7, H–C1′, H_2C2', H_2C4', H_2C5', H_2C6'), 0.93 (s, 9 H, $(H_3C)_3C$–C2); ^{13}C NMR ($CDCl_3$) δ 210.69, *210.46* (C3′), 176.92 (C4), 104.64, *104.16* (C2), 73.67 (C5), 57.42 (C8), *45.52*, 45.33 (C2′), *43.01*, 42.06 (C2′), 41.39, *41.26* (C6′), 36.42 (C–C2), *32.89*, 31.91 (C6), 25.99 (C5), 25.62, *25.16* (C1′), 24.95, *24.84* (C7), 24.47 ($(H_3C)_3C$); MS 222 (M^+ −57, 14.3), 182 (23.9), 166 (100), 85 (25.8), 83 (40.4). Anal. Calcd for $C_{16}H_{25}NO_3$ (279.36): C, 68.79; H, 9.02; N, 5.01. Found: C, 68.86; H, 8.86; N, 4.98.

(2*R*,5*R*)-5-(1′-Benzyl-2′-oxo-1′,2′,3′,4′-tetrahydro-4′-pyridyl)-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (26). From *N*-benzylpyridone (1 g, 5.5 mmol) and 0.91 g (5 mmol) of **2** was obtained after flash chromatography of the crude product with pentane/ether (1:1, R_f 0.33) 0.92 g (50%) of **26** as a yellow oil: $[\alpha]^{25}_D$ +111.9° (*c* 1.8; $CHCl_3$); IR (film) 2960 (m), 2875 (m), 1770 (s), 1665 (s); ^1H NMR ($CDCl_3$) δ 7.22 (br s, 5 H, arom), 6.06 (dd, $J_{6'5'}$ = 7.5 Hz, $J_{6'4'}$ = 1.5 Hz, 1 H, H–C6′), 4.98 (dd, $J_{5'6'}$ = 7.5 Hz, $J_{5'4'}$ = 3 Hz, 1 H, H–C5′), 4.58 (s, 2 H, benzyl), 4.10 (s, 1 H, H–C2), 2.92–2.59 (m, 4 H, H_2C8, H_2C3'), 2.24–1.01 (m, 5 H, H–C4, H_2C6, H_2C7), 0.83 (s, 9 H, $(H_3C)_3C$–C2); MS 267 (M^+ − 101, 0.6), 186 (1.2), 185 (1.2), 182 (1.0), 83 (100). Anal. Calcd for $C_{22}H_{28}N_2O_3$ (368.46): C, 71.71; H, 7.66; N, 7.60. Found: C, 71.58; H, 7.56; N, 7.45.

(2*R*,5*R*)-2-*tert*-Butyl-5-((nitromethyl)(3′,4′-dimethoxyphenyl)-methyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (27). To a cold solution of the enolate (10 mmol) **3**, prepared according to the general procedure, was added 2.30 g (11 mmol) of 3,4-dimethoxy-ω-nitrostyrene (in 20 mL of THF). Crystallization of the crude product from methanol gave 1.57 g (40%) of **27** as yellow crystals: diastereomeric ratio 85:15; mp 158–160 °C; $[\alpha]^{25}_D$ −2.1° (*c* 0.7; $CHCl_3$); IR ($CHCl_3$) 2960 (m), 1765 (s); ^1H NMR ($CDCl_3$) δ 7.10–6.66 (m, 3 H, arom), 5.60–4.65 (m, 2 H, H_2C–NO_2), 4.17/ *4.14* (s, 1 H, H–C2), 4.83 and 4.80 (s, each 3 H, 2 H_3C–O), 2.87–1.27 (m, 5 H, H_2C8, H_2C6, H-C1′, H_2C7), 0.98/*0.78* (s, 9 H, $(H_3C)_3C$); ^{13}C NMR ($CDCl_3$) δ 176.03, *175.80* (C2), 149.15, 148.88, *127.74*, 127.04, *122.28*, 121.14, 114.03, *113.16*, *111.46*, 110.88 (arom), 104.37, *103.75* (C2), 77.62, 75.05, 73.30 (C8, C2′, C1′), *56.38*, 56.02, 55.95, 55.80 (C5, 2 H_3CO), *49.88*, 48.72 (C6), 36.60 (C–C2), *36.11*, 32.46 (C7), 24.50, *24.16* ($(H_3C)_3C$); MS 393 (M^+ + 1, 0.4), 299 (5), 284 (13), 183 (13), 182 (100). Anal. Calcd for $C_{20}H_{28}N_2O_6$ (393.45): C, 61.05; H, 7.43; N, 7.12. Found: C, 60.96; H, 7.41; N, 6.94.

(2*R*,5*R*)-5-Acetyl-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (28). In a 5-mmol run, acetic anhydride (0.56 g, 5.5 mmol) and 0.91 g (5 mmol) of **2** were used to give after the usual workup and crystallization from ether 0.9 g (80%) of **28**: mp 85 °C; $[\alpha]^{25}_D$ +14.84° (*c* 5; $CHCl_3$); IR (film) 2960 (m), 1780 (s), 1720 (s); ^1H NMR ($CDCl_3$) δ 4.33 (s, 1 H, H–C2), 3.30–2.83 (m, 2 H, H_2C8), 2.31 (s, 3 H, CH_3), 2.25–1.53 (m, 4 H, H_2C6, H_2C7), 0.91 (s, 9 H, $(H_3C)_3C$–C2); MS 182 (M^+ − 43, 2.5), 181 (6.7), 125 (8.6), 124 (100), 96 (11.5). Anal. Calcd for $C_{12}H_{19}NO_3$ (225.27): C, 63.98; H, 8.50; N, 6.22. Found: C, 63.87; H, 8.46; N, 6.18.

(2*R*,5*R*)-2-*tert*-Butyl-5-benzoyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (29). Methyl 3,4-dimethoxybenzoate (1 g, 5.5 mmol) and 0.91 g (5 mmol) of **2** were used. Because of the instability of the product, spectroscopic data could be determined only of the crude material **29**: yield, 1.45 g (80%); IR (film) 1780 (s), 1670 (m); ^1H NMR ($CDCl_3$) δ 7.95 (dd, *J* = 1.5 Hz, *J* = 9 Hz, 1 H, H–C6′), 7.75 (d, *J* = 1.5 Hz, 1 H, H–C2′), 6.87 (d, *J* = 9 Hz, 1 H, H–C5′), 4.52 (s, 1 H, H–C2), 3.93 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.63–2.93 (m, 2 H, H_2C8), 2.66–2.10 (m, 2 H, H_2C6), 2.03–1.53 (m, 2 H, H_2C7), 0.88 (s, 9 H, $(H_3C)_3C$–C2).

(2*R*,5*R*)-2-*tert*-Butyl-5-(methoxycarbonyl)-1-aza-3-oxabicyclo-[3.3.0]octan-4-one (30). From methyl chloroformate (0.52 g, 5.5 mmol) and 0.91 g (5 mmol) of **2** a yield of crude product **30** of 1 g (85%) was obtained. Due to the instability of **30**, only the IR and NMR spectrum of unpurified material were measured: IR (film) 2960 (s), 1790 (s), 1750 (s); ^1H NMR ($CDCl_3$) δ 4.38 (s, 1 H, H–C2), 3.78 (s, 3 H, H_3CO), 3.47–2.80 (m, 2 H, H_2C8), 2.67–1.40 (m, 4 H, H_2C6, H_2C7), 0.95 (s, 9 H, $(H_3C)_3C$–C2); MS 210 (M^+ − 31, 2.4), 197 (8.2), 192 (36.1), 140 (100), 138 (12.1).

(*R*)-2-Benzylproline (31). To a solution of 10 mL of 48% aqueous HBr was added 0.55 g (2 mmol) of **10**, and the mixture was refluxed for 12 h. The solution was subjected to cation exchange chromatography on 20 g of Dowex 50W resin. Elution with 400 mL of 2 N ammonia and subsequent removal of water gave 0.3 g (77%) of **31**: $[\alpha]^{25}_D$ −19.25° (*c* 2.7; H_2O); IR (KBr) 3420 (m), 1625 (s); ^1H NMR (D_2O) δ 7.23 (s, 5 H, arom H), 3.07 (d, *J* = 12 Hz, 1 H, benzyl), 2.70 (d, *J* = 12, 1 Hz, benzyl), 2.77 (m, 2 H, H_2C5), 2.10 (m, 1 H, H–C3), 1.67 (m, 3 H, H–C3, H_2C4).

(*R*)-2-Benzylproline Dimethylamide (33). A solution of 10 mmol of lithium dimethylamide in 30 mL of THF/7 mL of hexane was cooled to −78 °C and a solution of 1.36 g (5 mmol) of **9** in 20 mL of THF was added. After the mixture was stirred for 1 h, the solution was partitioned between dichloromethane and water. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. Flash chromatography of the crude product with ether/triethylamine (9:1) and subsequent Kugelrohr distillation gave 0.49 g (43%) of **33** as a colorless oil: bp 170 °C (0.1 mm); $[\alpha]^{25}_D$ −52.4° (*c* 2.2; $CHCl_3$); IR (film) 3340 (m), 2960 (s), 1630 (s), 1500 (s); ^1H NMR ($CDCl_3$) δ 7.20 (s, 5 H, arom), 3.36–2.39 (m, 4 H, H_2C5, benzyl), 3.01 (br s, 6 H, $CONCH_3$), 2.26–1.03 (m, 5 H, H_2C3, H_2C4, NH); MS 233 (M^+ + 1, 1.0), 161 (32.3), 160 (100), 141 (82.5), 91 (39.1). Anal. Calcd for $C_{14}H_{20}N_2O$ (232.32): C, 72.38; H, 8.68; N, 12.06. Found: C, 72.53; H, 8.93; N, 12.08.

(*R*)-2-Benzylproline Methylamide (34). A solution of 20 mmol of lithium methylamide in 30 mL of THF/7 mL of hexane was cooled to −78 °C and a solution of 2.8 g (10 mmol) of **9** in 25 mL of THF was added. After the mixture was stirred for 1 h, the solution was partitioned between dichloromethane and water. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. Kugelrohr distillation gave 2 g (90%) of **34**: bp 165 °C (0.05 mm); mp 68–69 °C; $[\alpha]^{25}_D$ +11.85° (*c* 1.8; $CHCl_3$); IR ($CHCl_3$) 3350 s, 2980 s, 1650 s, 1520 s; ^1H NMR ($CDCl_3$) δ 7.61 (br s, 1 H, CONH), 7.22 (m, 5 H, arom), 3.46 (d, *J* = 13.5 Hz, 1 H, benzyl), 3.13–2.68 (m, 2 H, H_2C5), 2.65 (d, *J* = 6 Hz, 3 H, CH_3), 2.45 (d, *J* = 13.5 Hz, 1 H, benzyl), 2.36–1.43 (m, 5 H, H_2C3, H_2C4, NH); MS 189 (M^+ − 29, 1.1), 161 (12.8), 160 (100), 127 (12.6), 91 (18.0). Anal. Calcd for $C_{13}H_{18}N_2O$ (218.29): C, 71.53; H, 8.31; N, 12.31. Found: C, 71.25; H, 8.03; N, 12.49.

(*R*)-2-(1′-Hydroxybenzyl)proline Amide (35). A solution of 10 mmol of lithium amide in 30 mL of THF/7 mL of hexane was cooled to −78 °C and a solution of 1.45 g (5 mml) of **7** in 20 mL of THF was added. After the mixture was stirred for 1 h, the solution was partitioned between dichloromethane and water. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. Kugelrohr distillation of the crude product gave 0.5 g (45%) of **35**: bp 190 °C (0.05 mm); $[\alpha]^{25}_D$ −31.5° (*c* 4.7; $CHCl_3$); IR ($CHCl_3$) 3505 (s), 3360 (s), 2980 (s), 2880 (s), 1660 (s); ^1H NMR ($CDCl_3$) δ 7.60–7.13 (m, 6 H, arom, CONH), 5.90 (br s, 1 H, NH), 4.95, 4.76 (s, 1 H, benzyl, 5.2:1), 3.44 (br s, 2 H, OH, NH), 2.66 (t, 2 H, H_2C5), 2.38–1.78 (m, 2 H, H_2C3), 1.68–1.33 (m, 2 H, H_2C4); MS 202 (M^+ − 18, 1.2), 106 (95.7), 105 (95.6), 77 (100), 70 (76.4). Anal. Calcd for $C_{12}H_{16}N_2O_2$ (220.27): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.33; H, 7.31; N, 12.62.

(*R*)-2-Benzyl-2-(hydroxymethyl)-1-neopentylpyrrolidine (36). A solution of 0.54 g (2 mmol) of **9** in THF was treated with $LiAlH_4$ (0.3 g, 6 mmol) and the resulting suspension refluxed for 1 h. The mixture was then cooled with an ice bath, quenched by the addition of water, and filtered. The filter pad was washed with several small portions of THF, and the filtrate was concentrated in vacuo furnishing 0.45 g (87%) of the amine **36**. Kugelrohr distillation gave a colorless oil of **36**: bp 165 °C (0.1 mm); $[\alpha]^{25}_D$ −17.15° (*c* 2.04; $CHCl_3$); IR (film) 3460 (s), 2460 (s), 2370 (s), 1950 (w), 1880 (w), 1810 (w), 1600 (w); ^1H NMR ($CDCl_3$) δ 7.36–6.98 (m, 5 H, arom), 3.53–2.96 (m, 3 H, H_2CO, OH), 2.68–2.40 (m, 2 H, H_2C5), 2.60 (s, 2 H, NCH_2), 2.53 (d, *J* = 13.5 Hz, 1 H, benzyl), 2.19 (d, *J* = 13.5 Hz, 1 H, benzyl), 1.83–1.46 (m, 4 H, H_2C3, H_2C4), MS 262 (M^+ + 1, 0.5), 204 (29.4), 170 (100), 100 (48.1), 91 (32.3). Anal. Calcd for $C_{17}H_{27}NO$ (261.39): C, 78.11; H, 10.41; N, 5.36. Found: C, 77.96; H, 10.20; N, 5.35.

(*R*)-2-Acetyl-2-benzylpyrrolidine (38). To a solution of 1.36 g (5 mmol) of **9** in 30 mL of THF was added 6.3 mL of a 1.6 M solution of methyllithium in ether at −78 °C. After the mixture was stirred for 1 h, the reaction mixture was partitioned between dichloromethane and water. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo and 1.2 g of the hemiacetal **37** were obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.61 (m, 2 H, arom), 7.33 (m, 3 H, arom), 4.31 (s, 1 H, H–C2), 1.57 (s, 1 H, H_3C–C4), 1.10 (s, 9 H, $(H_3C)_3C$–C2); Kugelrohr distillation gave 0.90 g (88%) of the amino ketone **38** as a colorless oil: bp 100 °C (0.05 mm); $[\alpha]^{25}_D$ −60.3° (*c* 7.0, $CHCl_3$); IR (film) 3340 (m), 2980 (s), 2860 (s), 1700 (s), 1600 (m); ^1H NMR ($CDCl_3$) δ 7.22 (s, 5 H, arom), 3.13 (d, *J* = 13.5 Hz, benzyl H), 2.83 (d, *J* = 13.5 Hz, benzyl H), 3.00–2.73 (m, 2 H, H_2C5), 2.48 (s, 1 H, HN), 2.13 (s, 3 H, CH_3), 2.16–1.43 (m, 4 H, $CH_2$3, $CH_2$4); MS 160 (M^+ − 43, 100), 112 (80), 91 (36.3). Anal. Calcd for $C_{13}H_{17}NO$ (203.27): C, 76.81; H, 8.43; N, 6.89. Found: C, 76.69; H, 8.58; N, 6.72.

(*R*)-2-Benzoyl-2-benzylpyrrolidine (39). A solution of 1.36 g (5 mmol) of **9** in 30 mL of THF was combined at −78 °C with a benzene solution of phenyllithium (7.1 mL, 10 mmol). After the mixture was stirred for 1 h, it was partitioned between dichloromethane and water, the organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. Kugelrohr distillation gave 0.93 g (70%) of **39**: bp 190 °C (0.05 mm); $[\alpha]^{25}_D$ −35.16° (*c* 5; $CHCl_3$); IR (film) 3320 (m), 2980 (s),

1660 (s); ^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2 H, arom), 7.43 (m, 3 H, arom), 7.10 (m, 5 H, arom), 3.35 (d, J = 13.5 Hz, 1 H, benzyl), 3.06 (d, J = 13.5 Hz, 1 H, benzyl), 3.03-2.70 (m, 2 H, H_2C5), 2.46-1.53 (m, 4 H, H_2C3, H_2C4); MS 174 ($M^+ - 91$, 80), 160 (100). Anal. Calcd for $C_{18}H_{19}NO$ (265.33): C, 81.47; H, 7.22; N, 5.28. Found: C, 81.33; H, 7.39; N, 5.08.

(±)-2-*tert*-Butyl-1-aza-3-oxabicyclo[3.2.0]heptan-4-one (41). According to the procedure described above for the preparation of compound **2**, 10 g (100 mmol) of L- or (*S*)-2-acetidinecarboxylic acid and 60 mL of pivalaldehyde were condensed during 6 days and 9 g (54%) of racemic **41** were obtained as a yellow oil: bp 90 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) δ 4.53 (s, 1 H, H-C2), 4.16-3.36 (m, 3 H, H_2C7, H-C5), 3.03-2.03 (m, 2 H, H_2C6), 0.89 (s, 9 H, $(H_3C)_3C$-C2).

(2*R*,5*R*)-2-*tert*-Butyl-1-aza-3-oxa-7-thiabicyclo[3.3.0]octan-4-one (43). According to the procedure described for the preparation of compound **2**, 19.0 g (143 mmol) of **42**[34] and 100 mL of pivalaldehyde were condensed during 48 h. After crystallization from ether/pentane 22.4 g (78%) of **43** were obtained as pale yellow crystals. The product is very sensitive to moisture: mp 62 °C; $[\alpha]^{20}_D$ +86.0° (*c* 0.15; $CHCl_3$); IR (KBr) 2950 (m), 2870 (w), 1785 (s); ^{1}H NMR ($CDCl_3$) δ 4.47 (s, 1 H, H-C2), 4.30-3.93 (m, 3 H, H_2C8, H-C5), 3.57-3.03 (m, 2 H, H_2C6), 0.97 (s, 9 H, $(H_3C)_3C$-C2); MS 201 (M^+, 11), 146 (89), 100 (45), 96 (35), 54 (100). Anal. Calcd for $C_9H_{15}NO_2S$ (201.27); C, 53.70; H, 7.51; N, 6.96; S, 15.93. Found: C, 63.46; H, 7.57; N, 6.96; S, 15.80.

(*R*)-2-*tert*-Butyl-*N*-((methylthio)methyl)-4-methylidene-5-oxazolidinone (44). To a solution of 20.0 g (100 mmol) of **43** in 180 mL of THF stirred at -90° was added 120 mL of a 0.93 M LDA solution in THF/hexane 1:3. After the mixture was stirred for 30 min at -78 °C, 12 mL (188 mmol) of methyl iodide were added, and the temperature was allowed to rise to 0 °C overnight. The resulting mixture was partitioned between dichloromethane and water. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. Recrystallization from ether gave 20.1 g (94%) of **44** as pale yellow crystals: mp 29 °C; bp 140 °C (0.1 mm); $[\alpha]^{25}_D$ -277° (*c* 1.6; $CHCl_3$); IR ($CHCl_3$) 2960 (m), 1775 (s); ^{1}H NMR ($CDCl_3$) δ 5.17 (s, 1 H, H-C2), 5.04 (d, J = 2 Hz, 1 H, olefin), 4.65 (d, J = 13 Hz, 1 H, H_2C-N), 4.43 (d, J = 2 Hz, 1 H, olefin), 4.21 (d, J = 13 Hz, 1 H, H_2C-N), 2.13 (s, 3 H, H_3C-S), 0.96 (s, 9 H, $(H_3C)_3C$-C2); MS 215 (M^+, 8), 168 (21), 158 (12), 82 (10), 61 (100). Anal. Calcd for $C_{10}H_{17}NO_2S$ (215.31): C, 55.78; H, 7.96; N, 6.51; S, 14.89. Found: C, 56.11; H, 8.17; N, 6.85; S, 14.71.

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Supplementary Material Available: X-ray crystal structure determination and tables of *x*, *y*, *z*, and *U* values and bond lengths and angles for **7**, and a stereoview of the unit cell (6 pages). Ordering information is given on any current masthead page.

Structure and Conformation of 5-Methylarabinosylcytosine, a Potential Antiviral Nucleoside[1]

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Abstract: The three-dimensional structure of 1-β-D-5-methylarabinosylcytosine hydrate, a potential antiviral nucleoside, was determined by X-ray crystallography. The crystals belong to the orthorhombic space group $P2_12_12_1$ and the cell dimensions are a = 7.472 (1), b = 11.950 (1), and c = 13.723 (1) Å. Intensity data were measured on a diffractometer and the structure was determined by direct methods. Least-squares refinement, which included all hydrogen atoms, converged at R = 0.028 for 1457 observed reflections. The pyrimidine ring is significantly nonplanar and the methyl substitution at C(5) causes that atom to be pulled away from the center of the ring. The conformation about the glycosyl bond is anti with χ_{CN} = 22.6°. The arabinose ring is in an envelope conformation with a C(2') endo (^2E) pucker. The bond lengths and bond angles in the ring are discussed in relation to the ring's conformation and configuration.

Several arabinonucleosides are known to possess antiviral and/or anticancer properties. Arabinofuranosylcytosine (ara-C) is the mainstay of the treatment of acute myeloblastic leukemia in adults.[3] Arabinofuranosyladenine (ara-A, vidarabine) and arabinofuranosylthymine (ara-T) show activity against herpes and vaccinia viruses.[4,5] 2'-Fluoro-5-iodoarabinofuranosylcytosine (FIAC) was found to be especially capable of suppressing the replication of various strains of herpes simplex virus types 1 and 2, as well as of herpes zoster and cytomegalovirus.[6] When an

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