the steering effect of the cation is less pronounced and mixtures of cis/trans isomers result. However, these speculations need to be consolidated by further experiments including other electrophiles and under variation of reaction conditions.

The easy availability of diverse 4-substituted 1,2-oxazines such as **2** with defined stereochemistry has important synthetic consequences in light of the ring-opening reactions of these heterocycles.[15]

Acknowledgment. This work was generously supported by the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and the Karl-Winnacker-Stiftung (Hoechst AG).

Registry No. **1**, 109925-98-6; *cis*-**2a**, 115117-93-6; *trans*-**2a**, 115117-94-7; *cis*-**2b**, 115117-95-8; *trans*-**2b**, 115117-96-9; *cis*-**2c**, 115117-97-0; *trans*-**2c**, 115117-98-1; *cis*-**2d**, 115117-99-2; *trans*-**2d**, 115118-00-8; *cis*-**2e**, 115118-01-9; *trans*-**2e**, 115118-02-0; *cis*-**2f**, 115118-03-1; *trans*-**2f**, 115118-04-2; *cis*-**2g** (diastereomer 1), 115118-05-3; *cis*-**2g** (diastereomer 2), 115183-53-4; *trans*-**2g** (diastereomer 1), 115183-54-5; *trans*-**2g** (diastereomer 2), 115183-55-6.

(15) Products **2b** and **2d** could be ring opened analogously to reactions described in ref 1h. For related ring opening reactions of isoxazolines, see ref 4a.

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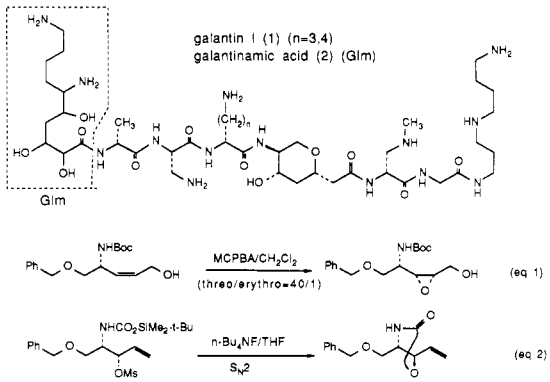
Synthesis and Absolute Structure of Galantinamic Acid

Summary: The structure of galantinamic acid (**2**) has been confirmed to be (2*R*,3*S*,5*S*,6*R*)-**25** by the stereoselective synthesis of each of the eight diastereomers derived from L-lysine; total synthesis of the natural form was accomplished by starting from D-lysine.

Sir: Galantin I (**1**), isolated from a culture broth of *Bacillus pulvifaciens*, has received considerable attention owing to its potent antibacterial activity.[1] The structure of **1**,[2] elucidated by chemical degradation and partly by synthesis, contains a new amino acid named galantinamic acid (**2**)[3] having four chiral centers, of which the stereochemistry remained to be determined. In conjunction with the studies toward the total synthesis of **1**,[2c] we began the structure determination of **2** via the stereoselective syntheses of the eight diastereomers from L- or D-lysine.

Since the primary structure of **2** possesses either a threo or an erythro 1,2-amino hydroxy system[4] at C5 and C6, the stereoselective synthesis of each isomer plays a key role in this study. Initially, we examined an epoxidation of the



(hydroxymethyl)-(*Z*)-allylamine with *m*-chloroperbenzoic acid (MCPBA) and found that the reaction provides the threo epoxide in a highly stereoselective manner (eq 1).[5] On the other hand, the erythro isomer can be prepared, enantiospecifically, from the threo mesylate via fluoride ion treatment of the silyl carbamate derived from *tert*-butyl carbamate (*t*-Boc) (eq 2).[6] On the basis of these methods, the syntheses of the eight diastereomers of **2** starting from L-lysine were carried out as follows.

Synthesis of the Four Diastereomeric Unsaturated Esters. Amino alcohol **3**, prepared from N^{α}-Boc-N^{ϵ}-Z-L-lysine, was converted to the (*Z*)-allyl alcohol **4** [three steps, 65%; (i) SO_3–pyridine, (ii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$/$KN(SiMe_3)_2$,[7] and (iii) i-$Bu_2AlH/BF_3{\cdot}OEt_2$[8]], which upon treatment with MCPBA gave the threo epoxide **5** (97%; threo/erythro = 40/1) (Scheme I). Regioselective epoxide opening of **5** with $LiAlH_4$ and successive protection of the resulting imino diol **6** furnished silyl ether **9** (three steps, 60%). It was necessary to introduce a *t*-Boc group at the N^{ϵ} position in place of the Z group at this stage because of subsequent chemical transformations and for the final comparison with the natural N^{α},N^{ϵ}-di-Boc derivative. It should be noted that this was carried out in one pot under hydrogenation conditions (H_2/Pd–C, MeOH) in the presence of di-*tert*-butyl dicarbonate (Boc_2O) to yield **10** in 93% yield.[9]

Following the method shown in eq 2, we next examined an inversion of the configuration at C3. Successive treatment of the mesylate **8**, prepared from **7** ($MsCl/Et_3N$), with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)[4a,10] and n-Bu_4NF provided the cyclic carbamate **11** (93%) where the reaction proceeded completely in an S_N2 manner.[6] Conversion of **11** into **12**, an isomeric form of **10**, was carried out by the following sequence of reactions: (i) *dl*-10-camphorsulfonic acid (CSA)/MeOH, (ii) H_2/Pd–C, (iii) $Ba(OH)_2$, (iv) Boc_2O, (v) TBSCl/imidazole, and (vi) $CSA/(CH_3)_2C(OCH_3)_2$; 50% overall yield.[11] Thus, with diastereomeric **10** and **12** in hand, their conversions

(1) Shoji, J.; Sakazaki, R.; Wakishima, Y.; Koizumi, K.; Mayama, M.; Matsuura, S. *J. Antibiot.* **1975**, *28*, 122.

(2) (a) Ando, T.; Terashima, S.; Kawata, M.; Teshima, T.; Wakamiya, T.; Shiba, T. *Peptide Chemistry 1980*; Okawa, K., Ed.; Protein Research Foundation: Osaka, 1981; p 113. (b) Wakamiya, T.; Ando, T.; Teshima, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 142. (c) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587.

(3) Wakamiya, T.; Terashima, S.; Kawata, M.; Teshima, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1422.

(4) For the syntheses of 1,2-amino hydroxyl systems from α-amino acids as the chiral source, see: (a) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1987**, *28*, 3987. (b) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. Other references are cited therein.

(5) (a) Hori, K.; Ohfune, Y. Presented at the 54th Annual Meeting of the Chemical Society of Japan, Tokyo, 1987; Abstract Papers II, p 1033. (b) Similar results were reported independently; see: Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 311.

(6) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1986**, *28th*, 526.

(7) For *Z*-selective Horner–Emmons reactions, see: Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. A high *Z*/*E* ratio (more than 20/1) when this reaction condition was used was observed in all cases described in the text.

(8) Moriwake, T.; Hamano, S.; Miki, D.; Saito, S.; Torii, S. *Chem. Lett.* **1986**, 815.

(9) For further applications of this method, see: Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.*, in press.

(10) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543.

(11) The stereochemistry of **10** and **12** having an isomeric relationship at C3 was confirmed by NOE studies: a NOE (6.8% enhancement) between C3 and C4 protons in the five-membered ring of the erythro isomer **12** was observed, but no NOE was observed in the threo **10**.

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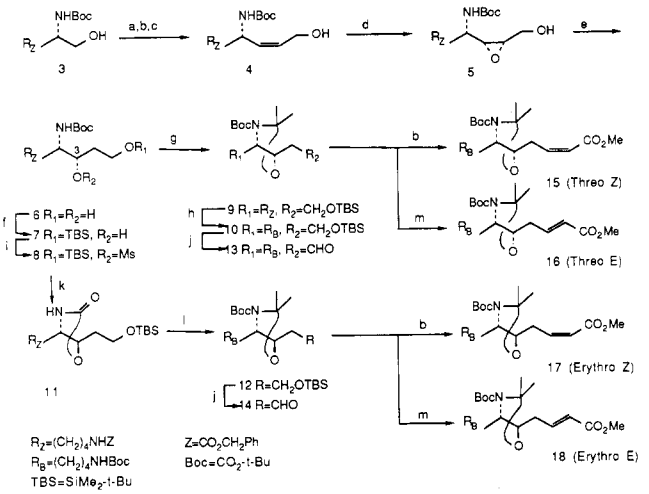
Scheme I[a]

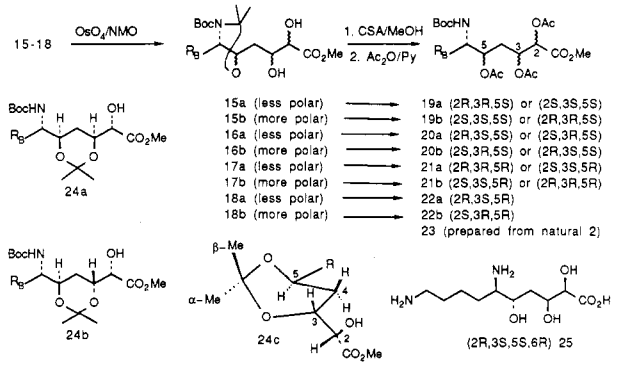


[a] (a) SO_3–pyridine, DMSO, room temperature, 10 min; (b) $(CF_3CH_2)_2P(O)CH_2CO_2Me$, $KN(SiMe_3)_2$, 18-crown-6, THF, −78 °C, 30 min;[7] (c) 2.2 equiv of $BF_3{\cdot}OEt_2$, 3 equiv of *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 1 h; (d) MCPBA, CH_2Cl_2, 0 °C, 14 h; (e) $LiAlH_4$, Et_2O, room temperature, 2.5 h; (f) *t*-$BuMe_2SiCl$ (TBSCl), imidazole, DMF, 0 °C, 2 h; (g) $(CH_3O)_2C(CH_3)_2$/acetone (1/1), cat. CSA, 60 °C, 3 h; (h) H_2/5% Pd–C, 1.2 equiv of Boc_2O, MeOH, room temperature, 16 h; (i) methanesulfonyl chloride (MsCl), Et_3N, CH_2Cl_2, 0 °C, 14 h; (j) (1) *n*-Bu_4NF, THF, 0 °C, 30 min; (2) 2.0 equiv of $(COCl)_2$, 2.7 equiv of DMSO, CH_2Cl_2, −78 °C, 15 min, −45 °C, 1 h, Et_3N, 0 °C, 20 min; (k) (1) 1.5 equiv of TBSOTf, 2.0 equiv of 2,6-lutidine, CH_2Cl_2, room temperature, 15 min; (2) 1.2 equiv of *n*-Bu_4NF, THF, 0 °C, 2 h; (l) (1) cat. CSA, MeOH, room temperature, 4 h; (2) H_2/5% Pd–C, MeOH, room temperature, 14 h; (3) $Ba(OH)_2$, 60% EtOH, 80 °C, 48 h; (4) Boc_2O, 0.05 equiv of Et_3N, dioxane, room temperature, 16 h; (5) same as step f; (6) same as step g; (m) $Ph_3P{=}CHCO_2Me$, benzene, room temperature, 16 h.

into the unsaturated esters **15–18** were carried out as follows. Removal of the silyl group of **10** with *n*-Bu_4NF followed by Swern oxidation gave the aldehyde **13**, which was converted into both *Z*[7] and *E* unsaturated esters **15** and **16**, stereoselectively; threo *Z* **15** (three steps, 67%) and threo *E* **16** (three steps, 77%). By repeating the above procedures, the erythro **12** was converted to the erythro *Z* and erythro *E* unsaturated esters **17** (68%) and **18** (86%), respectively.

Structure Determination of Galantinamic Acid (2). Introduction of a dihydroxyl moiety into the C2 and C3 trigonal centers was carried out by means of a catalytic osmium tetraoxide oxidation [OsO_4/*N*-methylmorpholine *N*-oxide (NMO)].[12] Each isomer **15–18** gave a 1:1 mixture of the corresponding diols **15a** and **15b**, **16a** and **16b**, **17a** and **17b**, and **18a** (less polar isomer; R_f 0.34, $CHCl_3$/MeOH = 95/5) and **18b** (more polar isomer; R_f 0.28, $CHCl_3$/MeOH = 95/5) in 85–91% yield (Scheme II). Each set of diols was separated by flash column chromatography and converted to the corresponding eight diastereomeric triacetates **19a,b–22a,b** [(i) CSA/MeOH and (ii) Ac_2O/pyridine] in order to carry out a spectroscopic comparison with the triacetate **23** prepared from natural **2** [(i) Boc_2O/Et_3N, (ii) CH_2N_2, and (iii) Ac_2O/pyridine]. Only the triacetate **22b** derived from the more polar isomer **18b** was found to be identical by 360-MHz ^1H NMR data with the natural isomer (see supplementary material). Thus, the relative stereochemistry at C5 and C6 of **2** can be assigned as the 5*R**,6*S** configuration, but the relative stereochemistry at C3 and C5 could be either 3*S**,5*R** or

Scheme II



3*R**,5*R**. Therefore, ^1H NMR studies of the acetonide **24b**, prepared from the more polar isomer **18b** [(i) CSA/MeOH and (ii) CSA/$(CH_3O)_2C(CH_3)_2$], were carried out. H,H-COSY and NOESY data of the acetonide **24b** revealed that this takes a pseudoboat conformation with a trans diequatorial relationship between the C3 and C5 substituents as shown in **24c** since the large *J* values between 3-H and 4α-H, and 4β-H and 5-H (*J* = 10 Hz) and a NOE between β-Me and 3-H, and α-Me and 5-H were observed.[13] Thus, the 2*S*,3*R*,5*R*,6*S* stereochemistry was unambiguously assigned to **22b** having either the natural or unnatural absolute configuration. Finally, the optical rotations of **22b** and the natural triacetate **23** were measured. It was found that each isomer showed opposite $[\alpha]^{26}_D$ values: **22b**, +8.41° (*c* 0.21, $CHCl_3$) and **23**, −8.67° (*c* 0.35, $CHCl_3$). Therefore, the absolute structure of **2** was assigned to be (2*R*,3*S*,5*S*,6*R*)-**25**. To complete this study, we synthesized the antipode of the erythro diol **18b** by starting from D-lysine.[14] Deprotection was carried out in three steps, (i) CSA/MeOH, (ii) 0.5 N NaOH, and (iii) CF_3CO_2H, to give **25**,[15] which showed identical spectroscopic data as well as physical constants with those of authentic **2**. The total synthesis of galantin I is in progress.

Acknowledgment. We thank Professor Koji Nakanishi, Director of the Suntory Institute for Bioorganic Research, for continuous encouragement. We are grateful to Professors T. Shiba and T. Wakamiya for informing us of unpublished results and providing an authentic sample of **2**. This work was supported in part by a grant-in-aid from the Ministry of Education, Science and Culture, Japan.

Supplementary Material Available: ^1H NMR data of the triacetates **19a,b–22a,b** and **23**, melting points, $[\alpha]_D$ values, and ^1H NMR data of the selected intermediates prepared from D-lysine, and ^1H NMR spectra of natural and synthetic **2** (7 pages).

(12) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947.

(13) The same studies were carried out in the acetonide **24a**, prepared from the less polar isomer **18a**: Chair conformation of **24a** with a cis diequatorial relationship between C3 and C5 substituents was deduced by the presence of the large *J* values between 3-H and 4β-H, and 4β-H and 5-H (*J* = 12 Hz); a NOE was observed between 3-H and 5-H. 360-MHz ^1H NMR ($CDCl_3$) data of **24a** and **24b**: **24a**, δ 1.34 (s, 3 H), 1.36 (s, 3 H), 1.44 (s, 18 H), 1.73 (ddd, 1 H, *J* = 12.0, 12.0, 12.0 Hz, 4β-H), 2.83 (d, 1 H, *J* = 9 Hz, OH), 3.10 (m, 2 H, 10-H_2), 3.53 (m, 1 H, 6-H), 3.90 (ddd, 1 H, *J* = 4.5, 4.5, 12.0 Hz, 5-H), 4.05 (dd, 1 H, *J* = 3.0, 9.0 Hz, 2-H), 4.19 (ddd, 1 H, *J* = 3.0, 3.0, 12.0 Hz, 3-H), 4.58 (br s, 1 H, NH), 4.62 (d, 1 H, *J* = 10 Hz, NH); **24b**, δ 1.25 (s, 3 H), 1.29 (s, 3 H), 1.44 (s, 18 H), 2.18 (ddd, 1 H, *J* = 6.5, 10.0, 13.0 Hz, 4α-H), 2.83 (d, 1 H, *J* = 8.5 Hz, OH), 3.11 (m, 2 H, 10-H_2), 3.57 (m, 1 H, 6-H), 3.70 (ddd, 1 H, *J* = 6.5, 6.5, 10.0 Hz, 5-H), 4.07 (dd, 1 H, *J* = 2.5, 8.5 Hz, 2-H), 4.13 (ddd, 1 H, *J* = 2.5, 6.0, 10.0 Hz, 3-H), 4.45 (d, 1 H, *J* = 10.0 Hz, NH), 4.57 (br s, 1 H, NH).

(14) Optical rotation of the triacetate **22b** synthesized from D-lysine: $[\alpha]^{26}_D$ −8.42° (*c* 0.55, $CHCl_3$).

(15) Obtained as the mono HCl salt by the following treatments: (i) Dowex 50Wx4 (elution with 10% NH_3) and (ii) adjustment at pH 6.5 with 0.01 M HCl: mp 203.0–205.0 °C dec; $[\alpha]^{26}_D$ −0.5° (*c* 0.4, 1 M HCl) [lit.[3] mp 207.5–209.0 °C dec; $[\alpha]^{22}_D$ −0.4° (*c* 0.5, 1 M HCl)].

Ordering information is given on any current masthead page.

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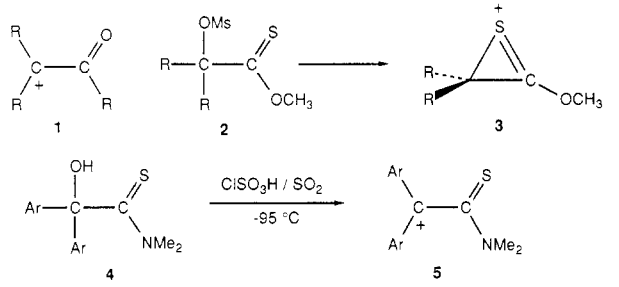
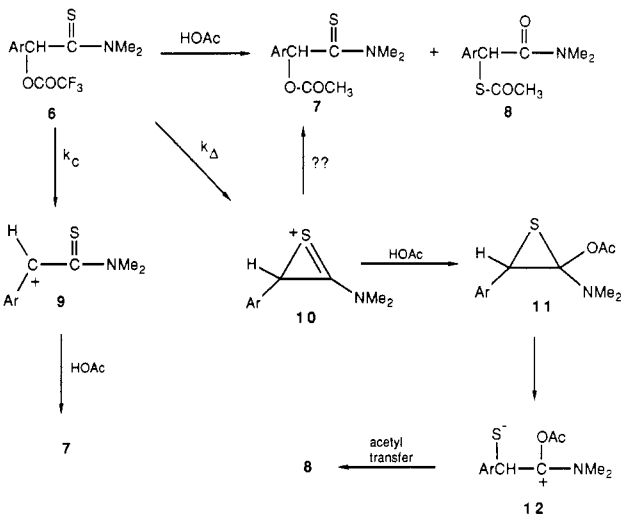
Carbocation Stabilization by the Thioamide Group

Summary: The thioamide group, $CSNMe_2$, when attached to a developing carbocationic center, can be a very effective carbocation stabilizing group. Stabilization occurs by either sulfur participation leading to the formation of cyclized ions or by extensive conjugative charge delocalization onto sulfur.

Sir: We have been interested in the mechanisms by which carbocations substituted with formally electron-withdrawing groups derive stabilization.[1] This interest is an outgrowth of the observation that many cations of type **1**, substituted with the carbonyl group can be generated with surprising ease.[2] A fundamental question concerns the nature of such cations. Are they open or closed ions? A previous study[3] led us to conclude that, unlike their carbonyl counterparts, thiocarbonyl esters of the type **2** react by way of the closed cations **3**. Recently it has been found that related thioamide substituted cations **5** can be formed under stable ion conditions.[4] We now report our findings on the behavior of certain thioamide substituted carbocations under solvolytic conditions.



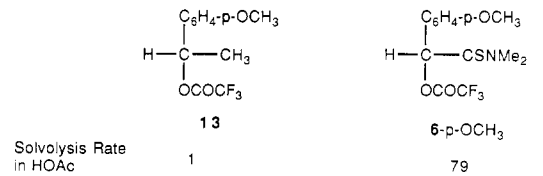
A series of trifluoroacetates **6** were prepared and reacted in acetic acid at room temperature where they were converted to products at convenient rates. Rate data are given in Table I. These substrates are considerably more reactive than the C=O analogues where mesylate derivatives are necessary to achieve convenient reactivity.[5] The products derived from acetolysis of **6** are the simple substitution product **7** and the rearranged product **8**. The ratio of these two products (Table II) is substituent dependent. The rearranged product **8** is suggested to arise via the k_Δ process which leads to the cyclized ion **10**.



Solvent capture at the carbon carrying the dimethylamino group followed by ring opening and acetyl group transfer would give the rearranged product **8**. This process is analogous to that suggested for the ester **2** where R = CH_3.[3] The simple substitution product **7** could be derived in principle from nucleophilic solvent opening at the benzylic position of the cyclized ion. Alternatively a competing k_c process, giving the open ion **9**, followed by solvent capture, would give this unrearranged product **7**.

A Hammett plot of the rate data (Figure 1) is not linear and indicative of a mechanistic changeover. Also of interest is the relatively small rate spread of only 1.1×10^3 despite substituents ranging from *p*-methoxy to 3,5-bis(trifluoromethyl). We have arbitrarily drawn a line connecting the *p*-CF_3 and the 3,5-$(CF_3)_2$ systems (ρ^+ value of −1.2). This region represents the area where the k_Δ process leading to cyclized ions **10** is dominant. The other line is arbitrarily drawn between the *p*-OCH_3 and the *p*-CH_3 substrates (slope of −2.4)[6] and represents the region where the k_c process leading to open ions of type **9** is dominant. This plot suggests that **6**-*p*-OCH_3 reacts mostly by the k_c process.

The most striking feature of the reaction of **6**-*p*-OCH_3 in acetic acid is the rate. The acetolysis rate of **6**-*p*-OCH_3 is 79 times faster than that of the α-methyl analogue, *p*-$CH_3OC_6H_4CH(CH_3)OCOCF_3$ (**13**). The $CSNME_2$ group, which is a potent carbanion stabilizing group,[7] therefore exceeds the methyl group in its ability to stabilize carbocations.



The *p*-nitrobenzoate **14**, on solvolysis in 80% aqueous acetone, gave exclusively the elimination product **15** presumably via the intermediacy of the corresponding thioamide substituted cation. Proton loss from this intermediate leads to the product **15**. The norbornyl system **16**

(1) For review and leading references on cations substituted with electron-withdrawing groups, see: (a) Bégué, J.-P.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207–212. (b) Gassman, P. G.; Tidwell, T. T. *Acc. Chem. Res.* **1983**, *16*, 279–285. (c) Creary, X. *Acc. Chem. Res.* **1985**, *18*, 3–8. (d) Tidwell, T. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 20–32.

(2) (a) Creary, X. *J. Am. Chem. Soc.* **1984**, 106, 5568–5577. (b) Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, 104, 4151–4162.

(3) Creary, X.; Mehrsheikh-Mohammadi, M. E. *J. Org. Chem.* **1986**, *51*, 7–15.

(4) Ablenas, F. J.; George, B. E.; Maleki, M.; Jain, R.; Hopkinson, A. C.; Lee-Ruff, E. *Can. J. Chem.* **1987**, *65*, 1800–1803.

(5) Creary, X.; McDonald, S. R.; Eggers, M. E. *Tetrahedron Lett.* **1985**, *26*, 811.

(6) This does not imply that the ρ^+ value for the k_c process is −2.4. The rate of **6**-*p*-CH_3 may well have a significant k_Δ component since it appears to fall in the region of the mechanistic change.

(7) α-Thioamide anions are readily formed. For representative examples, see: (a) Schuijl, P. J.; Bos, H. J. T.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 123. (b) Tamura, Y.; Furukawa, Y.; Mizutani, M.; Kitao, O.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 3631. (c) Tamura, Y.; Harada, T.; Iwamoto, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1978**, *100*, 5221.

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