correlations between $\Delta^1J_{CO,C1}$ values and $\sigma_R^+$. On the other hand, for electron-withdrawing groups, the similar and opposite contributions of the $\Delta\delta_{C1}$ and $\Delta\delta_{CO}$ terms could explain the very small, if any, $\Delta J$ values.

Further studies are in progress to better understand the nature of substituent effects on $^1J_{CO,C1}$ in benzoates, also through their theoretical simulation, at the INDO level, according to Ramsey's theory.[16] Moreover, in order to test if the results obtained herein for benzoates are just a consequence of minor conjugative interactions between the COOMe group and the aryl moiety, we have also undertaken an analogous study of $^1J_{CO,C1}$ in acetophenones, where vice versa effective conjugative interactions between the acetyl group and the ring have to be expected.[1a]

**Acknowledgment.** Financial support from MURST is gratefully acknowledged.

**Registry No.** **1a**, 1202-25-1; **1b**, 619-45-4; **1c**, 121-98-2; **1d**, 403-33-8; **1e**, 619-42-1; **1f**, 99-75-2; **1g**, 93-58-3; **1h**, 2967-66-0; **1i**, 1129-35-7; **1j**, 619-50-1; **1k**, 3609-53-8; **2a**, 141753-67-5; **2b**, 79909-92-5; **2c**, 37934-88-6; **2d**, 14659-60-0; **2e**, 90841-46-6; **2f**, 2282-84-0; **2g**, 14920-81-1; **2j**, 114820-16-5; **2k**, 114820-15-4.

(15) The dual-substituent-parameter treatment[12] of $\Delta\delta_{C1}$ for methyl 4-X-benzoates, attempted to dissect the polar and resonance effects of substituents, gives the best fit with the $\sigma_R^+$ resonance scale [$\Delta\delta_{C1}$ = 4.89 (±1.10)$\sigma_I$ + 8.82 (±0.37)$\sigma_R^+$ + 0.18 (±0.49) ($n$ = 11, $r$ = 0.995, $f$ = 0.09)]. The analogous treatment for **2** gives $\Delta\delta_{C1}$ = 5.13 (±1.72)$\sigma_I$ + 8.71 (±0.57)$\sigma_R^+$ + 0.13 (±0.73) ($n$ = 9, $r$ = 0.991, $f$ = 0.12). These results show that in either case the resonance contribution to $\Delta\delta_{C1}$ values is the dominant one for electron-donating substituents.

(16) Ramsey, N. F. *Phys. Rev.* **1953**, *91*, 303.

# Sequential Diastereoselective Addition and Allylic Azide Isomerization of *syn*- and *anti*-α-Azido-β-(dimethylphenylsilyl)-(*E*)-hex-4-enoates with Acetals: Asymmetric Synthesis of γ-Hydroxy-α-amino Acid Synthons

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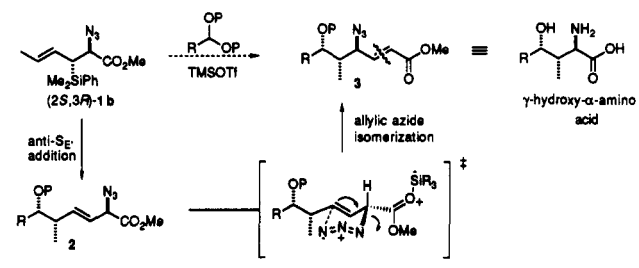
*Received May 12, 1992*

*Summary:* *syn*- and *anti*-methyl α-azido-β-(dimethylphenylsilyl)-(*E*)-hex-4-enoates (2*R*,3*R*)-**1a** and (2*S*,3*R*)-**1b** undergo highly diastereo- and enantioselective addition reactions with oxonium ions catalyzed by the action of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to generate α-azido-β,γ-unsaturated esters **2**, with well-defined 1,4- and 1,5-stereochemical relationships, and a subsequent stereospecific allylic azide isomerization generated 1,3-azido ethers **3**, synthetic equivalents of γ-hydroxy-α-amino acids.

Natural products that contain unusual γ-hydroxy-α-amino acid residues are being found in increasing numbers in a wide variety of structural types.[1] As a consequence of the growing importance of molecules containing these structural units, the development of new reaction methodology that provides a stereoselective approach to this class of compounds is becoming an active area of research.[2] In earlier reports we have described the results of investigations concerning the development of functionalized (*E*)-crotylsilanes as carbon nucleophiles in diastereoselective addition reactions to acetals and aldehydes. Those studies resulted in the development of a useful strategy for the asymmetric construction of homoallylic ethers[3] and tetrahydrofurans.[4] Herein we disclose our results of experiments intended to further explore the utility of related α-azido (*E*)-crotylsilanes, (2*R*,3*R*)-**1a**[5] and (2*S*,3*R*)-**1b**,[6] in a sequential Lewis acid catalyzed condensation–allylic azide isomerization reaction with acetals.

**Scheme I**




In 1960, Winstein had reported that allylic azides existed as an equilibrating mixture of two isomers, interconverting by a rapid isomerization at room temperature and that the rate of equilibration was insensitive toward solvent type.[7] Lacking a well-defined regio- and stereochemistry, the reaction has remained highly underdeveloped and no general approach to effecting a controllable, stereoselective isomerization has been reported. Recent examples of

(1) (a) *Theonellamide F*: Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Walchli, M. *J. Am. Chem. Soc.* **1989**, *111*, 2582–2588. (b) *Scytonemin-A*: Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298–1307. (c) Nikkomycins (Neopolyoxins): Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T. *Tetrahedron* **1982**, *38*, 1599–1608. (d) Review on polyoxins: Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333–352. (e) Hagenmaier, H.; Keckeisen, A.; Zahner, H.; Konig, W. A. *Liebigs Ann. Chem.* **1979**, 1494–1502.

(2) Synthetic studies on nikkomycins: (a) Hahn, H.; Heitsch, H.; Rathmann, R.; Zimmermann, G.; Bormann, C.; Zahner, H.; Konig, W. A. *Liebigs Ann. Chem.* **1987**, 803–807. (b) Barrett, A. G. M.; Dhanak, D.; Lebold, S. A.; Russell, M. A. *J. Org. Chem.* **1991**, *56*, 1894–1901. (c) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1991**, *56*, 4875–4884.

(3) (a) Aryl acetals: Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594–6600. (b) Hetero-substituted acetals: Panek, J. S.; Yang, M. *J. Org. Chem.* **1991**, *56*, 5755–5758.

(4) Aldehydes: Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868–9870.

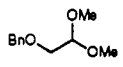
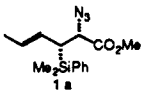
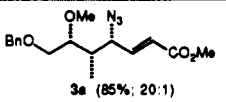
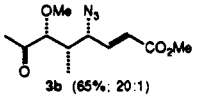
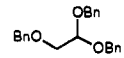
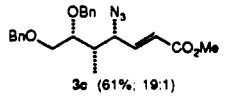
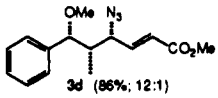
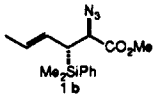
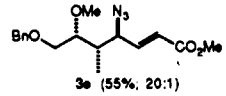
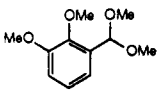
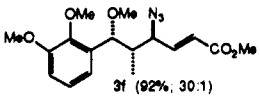
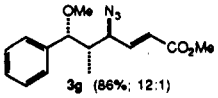
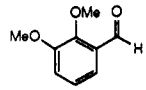
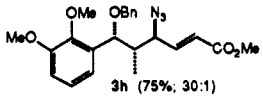
(5) syn-α-Azide **1a**: (a) Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3431–3438. (b) Sparks, M. A.; Panek, J. S. *Tetrahedron Lett.* **1991**, *33*, 4085–4088.

(6) anti-α-Azide **1b**: Panek, J. S.; Beresis, R.; Xu, F.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341–7344.

(7) Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956–5957.

0022-3263/92/1957-4063$03.00/0 

**Table I. Stereoselective Allylic Azide Isomerization**

| entry | acetal/aldehyde | silane | method[a] | 5,6-ratio major diastereomer[b] (%;[c] syn/anti[d]) |
|---|---|---|---|---|
| 1 |  |  1a | A |  3a (85%; 20:1) |
| 2 |  | 1a | A |  3b (65%; 20:1) |
| 3 |  | 1a | A |  3c (61%; 19:1) |
| 4 |  | 1a | B |  3d (86%; 12:1) |
| 5 |  |  1b | B |  3e (55%; 20:1) |
| 6 |  | 1b | A |  3f (92%; 30:1) |
| 7 |  | 1b | B |  3g (86%; 12:1) |
| 8 |  | 1b | B |  3h (75%; 30:1) |

[a] Method A: All reactions were run in $CH_2Cl_2$ (0.2–0.25 M) with 1.1 equiv of acetal and 1.1 equiv TMSOTf from −78 °C to −50 °C for 16–24 h. Method B: All reactions were run in $CH_2Cl_2$ (0.2–0.25 M) with 1.1 equiv of aldehydes and 2.0 equiv TMSOTf from −78 °C to 0 °C for 16–48 h in the presence of TMSOMe or TMSOBn (1.1 equiv). [b] The absolute stereochemistry of the major diastereomer assigned based on the anti addition ($S_E'$ mechanism) of the optically pure (*E*)-crotylsilanes to the C=OMe$^+$ π-bond (96% de); cf. ref 3. [c] All yields are based on pure materials isolated by chromatography on $SiO_2$. [d] Ratio of products was determined by $^1H$ NMR (400 MHz) operating at S/N ratio of >200:1.

allylic azide isomerizations are available which support this notion.[8]

This paper describes the utility of methyl α-azido-β-(dimethylphenylsilyl)-(*E*)-hex-4-enoates (2*R*,3*R*)-**1a** and (2*S*,3*R*)-**1b** in diastereoselective additions with acetals resulting in the construction of α,β-unsaturated-γ-azido esters **3**, synthetic equivalents of γ-hydroxy-α-amino acids.[9] Two sequential diastereoselective reactions describe this process; chiral allylsilane bond construction methodology produces the α-azido ester **2**, which is followed by a stereospecific allylic azide isomerization resulting in the formation of the α,β-unsaturated ester **3** (Scheme I).

We began the present study with the expectation that the illustrated silanes would show useful levels of diastereoselection in Lewis acid catalyzed additions to acetals.[3,4] In the initial discovery of the allylic azide isomerization, the (*E*)-crotylsilane **1a** was treated with TMSOTf (1.2 equiv) in the presence of α-(benzyloxy)acetaldehyde dimethylacetal in $CH_2Cl_2$ (0.25 M, −70 °C, 20 h). After being quenched with a solution of $NaHCO_3$ and extractive isolation, the α-azido ester **2** (R = $CH_2OBn$, P = Me) and the isomerized product **3a** were obtained as a 3:1 mixture, respectively (Scheme I). Chromatography of the crude reaction mixture on $SiO_2$ gel efficiently isomerized **2** to **3a** in 85% isolated yield as a single diastereomer (Table I, entry 1).[10,11] The mixture could also be isomerized by exposure to $BF_3{\cdot}OEt_2$ (0.1 equiv) in $CH_2Cl_2$ at room temperature.[12] Having verified an efficient, controllable allylic azide isomerization reaction of **1a**, we then examined the generality of this reaction with a series of acetals and (*E*)-crotylsilanes **1a** and **1b**. The results of those experiments describing the enantioselective condensation and subsequent isomerization are given in Table I. The data in the table show that both *syn*- and *anti*-α-azido-(*E*)-crotylsilanes **1a** and **1b** exhibit high levels of selectivity in reactions with a variety of structural types including α-keto and aryl acetals (entries 2 and 4).

In experiments designed to optimize the reaction conditions, we have determined that the enantioselective condensation reactions can be performed by the in situ generation of an oxonium ion according to the procedure of Markó.[13] Thus, combining equimolar quantities of the (*E*)-crotylsilane and aldehyde with 1.1 equiv of the trimethylsilyl ether, TMSOMe, or TMSOBn followed by TMSOTf (1.0–2.0 equiv) afforded the α,β-unsaturated esters **3d,e,g** and **h** (Table I). The synthetic utility of this process for the formation of γ-hydroxy-α-amnio acid synthons is further enhanced by the fact that the entire reaction sequence may be carried out in a single reaction vessel without the isolation of intermediate **2**.

The use of α-azido-(*E*)-crotylsilanes in diastereoselective addition reactions to acetals expands the scope of our developing chiral allylsilane bond construction methodology to include the production of γ-hydroxy-α-amino acid synthons and documents a stereoselective allylic azide isomerization. Further studies concerning the applications of these reagents will be reported in due course.

**Acknowledgment.** This work has been financially supported by the National Institutes of Health (CA47249).

**Supplementary Material Available:** Experimental procedures and spectral data for all reaction products as well as relative stereochemical proof of the azide isomerization products (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Recent reports of allylic azide isomerizations: (a) Safi, M.; Fahrang, R.; Sinou, D. *Tetrahedron Lett.* **1990**, *31*, 527–530. (b) Murahashi, S. I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227–230. (c) Murahashi, S. I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292–3303. (d) Askin, D.; Angst, C. Danishefsky, S. J. *J. Org. Chem.* **1985**, *50*, 5005–5007. (e) Hung, R. R.; Straub, J. A. Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 3849–3855. (f) VanderWerf, C. A.; Heisler, R. Y.; McEwen, W. E. *J. Am. Chem. Soc.* **1954**, *76*, 1231–1235.

(9) For a detailed report describing the asymmetric synthesis and synthon equivlency of α-azido carboxylic acid derivatives see: Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011–4030.

(10) (a) These findings are consistent with a stereospecific anti $S_E'$ process as previously reported: Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962–4963. (b) The relative stereochemistry of the isomerization products **3a** and **3e** has been shown to be consistent with a suprafacial migration of the azide group with respect to the olefin; see supplementary material for details.

(11) All new compounds were isolated as chromatographically pure materials and exhibited acceptable $^1H$ NMR, $^{13}C$ NMR, IR, MS, and HRMS spectral data.

(12) Attempts to isomerize azide **3** back to the starting allylic azide **2** by exposure to $BF_3{\cdot}OEt_2$ (1.1 equiv, $CH_2Cl_2$, reflux 24 h) were unsuccessful.

(13) Makhalfia, A.; Marko', I. E. *Tetrahedron Lett.* **1991**, *32*, 4779–4782.