3.30–3.40 (m, 1 H), 1.85–1.95 (m, 1 H).

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Registry No. 1, 115290-82-9; 2, 115290-83-0; 3a, 92610-81-6; 3b, 92693-35-1; 4, 115290-84-1; 5, 115290-85-2; 6, 115362-11-3; 7, 115290-86-3; 8, 115290-87-4; 9, 115290-88-5; $Ti(O\text{-}i\text{-}Pr)_4$, 546-68-9; (-)-(2S,3S)-2,3-epoxy-1-undecanol, 101976-99-2; (-)-(2S,3S)-2,3-epoxy-1-octanol, 89461-51-8; (-)-(2S,3R)-2,3-epoxy-1-hexanol, 89321-71-1; (+)-(2S,3R)-2,3-epoxy-1-hexanol, 92418-71-8; (-)-(2R,3R)-2,3-epoxy-1-cyclohexyl-1-propanol, 115362-12-4; (-)-(2S,3R)-2,3-epoxy-4-(benzyloxy)-1-butanol, 78513-07-2; (-)-(2S,3R)-2,3-epoxy-1-undecanol, 96249-61-5; 2,3-epoxy-2-tetradecyl-1-propanol, 88393-68-4; (-)-(2S,3S)-2,3-epoxycinnamyl alcohol, 104196-23-8; (+)-(2R,3R)-2,3-epoxy-4-bromocinnamyl alcohol, 115362-13-5.

New Maytansinoids: Reduction Products of the C(9) Carbinolamide

John A. Suchocki and Albert T. Sneden*

Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia 23284-2006

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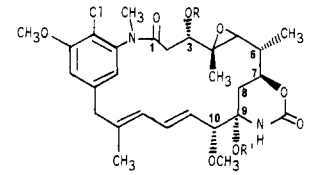
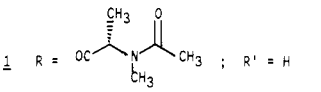
Ongoing research in our laboratory has been directed toward the preparation of derivatives of the maytansinoids, a class of naturally occurring potent antileukemic agents exemplified by maytansine (1).[1-4] In particular, we have focused our attention upon derivatives of the C3 and C9 positions. In the course of selecting a reducing agent for the efficient formation of maytansinol (2) from maytanbutine (3), one reagent, lithium borohydride in the presence of 10% lithium triethylborohydride,[5] was found to give a product, maytancarbutine[6] (4), that was modified only in the region of the C9 carbinolamide. Maysine (5), which lacks the C3 ester side chain, was reacted under the same conditions to give an analogous product, maycarsine[6] (6). Reactions of the borohydride reagent with a model compound 7 and the C9 methyl ether of maytanbutine (8) suggested a mechanism that involves hydrolysis of the carbinolamide followed by hydride addition to an intermediate ketone at C9.

In a typical reaction for the formation of 4, 3 was reduced with 10 equiv of lithium borohydride and 1 equiv of lithium triethylborohydride over the course of 36 h in THF. After workup, a 66% yield of 4 was obtained. In addition, a 20% yield of 6 was obtained and 5% of 3 was recovered. The product 4 was also obtained upon reaction of 3 with only lithium borohydride. However, yields were significantly lower and longer reaction times were required.

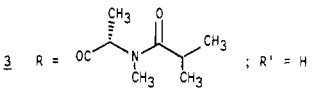
Microanalysis, the FAB mass spectrum, and the high-resolution electron-impact mass spectrum of 4 suggested a molecular formula of $C_{36}H_{52}ClN_3O_{10}$, which was consistent with a simple reduction of 3. In the HREIMS of 4, no ion was observed at m/z 658 ($[M - HNCO - H_2O]^+$) or m/z 485 as would be expected from a normal maytansinoid.[7] However, a significant ion was observed at m/z 678.3264 (3.86%, $C_{35}H_{51}ClN_2O_9$), indicative of a loss of only HNCO from the molecular ion of 4. Subsequent loss of the C3 ester gave an ion at m/z 505.2155. These data suggested that reduction of the carbinolamide of 3 had occurred to give 4 in which the C9-OH was less susceptible to elimination in the mass spectrometer.



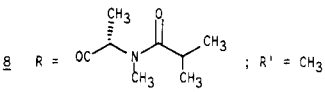


1 R = ; R' = H

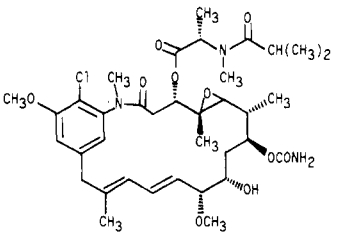
2 R = H ; R' = H



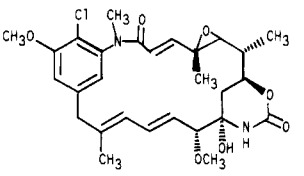
3 R = ; R' = H



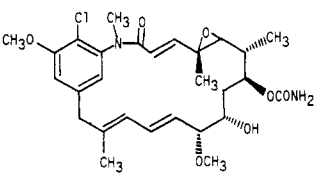
8 R = ; R' = CH_3



4



5



6

The ^1H NMR data for 4 also suggested that the borohydride mixture reacted selectively with the C9 carbinolamide of 3. The ^1H NMR spectra of 4 differed most notably from the spectra of 3 (Table I) in the absence of the C9-NH resonance and the presence of a new, two-proton singlet at 4.90 ppm, which shifted to 7.30 ppm when the spectrum was measured in acetone-d_6, and a new, one-proton doublet at 3.85 ppm. These data suggested that the carbinolamide ring had cleaved to give a carbamoyl group at C7 and a secondary hydroxyl group at C9. This conclusion was supported by the downfield shift of the C7-H multiplet and the upfield shifts of the resonances for C6-H, C6-CH_3, C10-H, and C10-OCH_3. The C10-H appeared as a doublet of doublets, confirming the presence of a hydrogen at C9. Additional evidence for the proton at C9 was found in the ^{13}C NMR spectrum of 4. A doublet

(1) Kupchan, S. M.; Komoda, Y.; Branfman, R. G.; Sneden, A. T.; Court, W. A.; Thomas, G. T.; Hintz, H. P. J.; Smith, R. M.; Karim, A.; Howie, G. A.; Verma, A. K.; Nagao, Y.; Daily, R. G., Jr.; Zimmerly, V. A.; Sumner, W. C. *J. Org. Chem.* **1977**, *42*, 2349.

(2) Sneden, A. T.; Beemsterboer, G. L. *J. Nat. Prod.* **1980**, *43*, 637.

(3) Sneden, A. T.; Sumner, W. C., Jr.; Kupchan, S. M. *J. Nat. Prod.* **1982**, *42*, 624.

(4) Kupchan, S. M.; Sneden, A. T.; Branfman, A. R.; Howie, G. A.; Rebhun, L. I.; McIvor, W. E.; Wang, R. W.; Schnaitman, T. C. *J. Med. Chem.* **1978**, *21*, 31.

(5) Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604.

(6) The trivial names for 4 and 6 were derived from the trivial names for the parent compounds 3 and 5 and are meant to imply the presence of the carbamoyl group at C7.

(7) The electron-impact mass spectra of maytansinoids bearing C3 esters typically do not show parent ions. Instead, an immediate loss of (HNCO + H_2O) resulting from the fragmentation of the carbinolamide gives an ion observed at $M^+ - 61$. Subsequent elimination of the C3 ester of maytansinoids then results in an ion at m/z 485.[1]

0022-3263/88/1953-4116$01.50/0

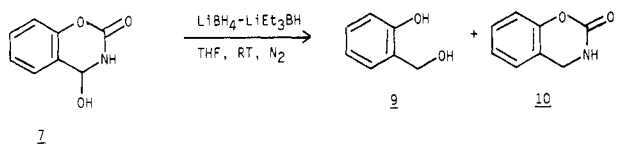


Figure 1.

Table I. Key ^{1}H NMR Resonances (ppm) for Maytansinoids 3–6 (J in Hz) in $CDCl_3$

proton	3	4	5	6
C6-H	1.47 m	1.43 m	1.64 m	1.60 m
C6-CH_3	1.29 d (6)	1.11 d (6)	1.34 d (7)	1.15 d (7)
C7-H	4.30 m	4.80 m	4.34 m	4.86 m
C7-$OCONH_2$		4.90 br s		4.76 br s
C8-H_α	1.20–1.30	1.16 m	1.15–1.30	1.34 m
C8-H_β	1.20–1.30	1.13 m	1.15–1.30	1.23 m
C9-H		3.89 dd (2,10)		3.89 dd (2, 10)
C9-NH	6.34 s		6.32 s	
C10-H	3.51 d (9)	3.40 dd (2, 9)	3.47 d (10)	3.39 dd (2, 10)
C10-OCH_3	3.35 s	3.29 s	3.33 s	3.29 s

at 71.5 ppm could be assigned to C9 and the typical C9 singlet at 81.5 ppm present in the spectrum of **3** was absent. These data were consistent with the structure of **4** as shown but did not establish the stereochemistry at C9.

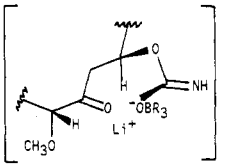
In order to examine the generality of this reaction, to simplify interpretation of the NMR data, and to establish the C9 stereochemistry, **5** was reduced under identical conditions to give **6**. As noted previously, **6** was also formed as the minor product in the reduction of **3**. The FAB mass spectrum of **6** showed a $[M + H]^+$ ion at m/z 505.2145 ($C_{27}H_{36}ClNO_6$ = 505.2242). Comparison of the ^{1}H NMR data for **6** to that for **5** (Table I) showed analogous trends to those described for **4** and established the structure of **6** as shown.

Examination of the homonuclear correlated (COSY) spectra of **4** and **6** facilitated determination of the stereochemistry at C9 (the stereochemistry at C7 was assumed to have remained unchanged). In particular, in the COSY spectrum of **6**, the C9-H doublet at 3.89 ppm was found to couple strongly (J = 10 Hz) to the C8-H_α resonance at 1.34 ppm but not to the C8-H_β resonance at 1.23 ppm. Examination of molecular models indicates that this is most likely when the C9-H is on the β face of the molecule. The small coupling (J = 2 Hz) between the C9-H and the C10-H, which is also on the β face of the molecule, confirms this assignment since models show that these two hydrogens are close to being coplanar. Analysis of the more complex COSY spectrum of **4**, using the above data for guidance, gave identical results. Therefore, the borohydride reagent reduces maytansinoids stereospecifically to give a C9 secondary alcohol with the S configuration.

In an attempt to elucidate the mechanism of the reduction, **7**, a less complex carbinolamide, was reduced with 1.1 equiv of the borohydride mixture (Figure 1). The major product of the reduction was found to be *o*-hydroxybenzyl alcohol (**9**) and the minor product was the cyclic carbamate **10**. Several mechanisms could account for this result, one of which would be abstraction of the carbinol hydrogen followed by loss of isocyanate and reduction of the salicylaldehyde anion to give **9**.

To determine if the presence of the C9 carbinol is required for this reduction, 9-*O*-methylmaytanbutine (**8**) was prepared and subjected to the reduction conditions. The reduced product, 9-*O*-methylmatancarbutine, was not observed and 29% of **8** was recovered. The remaining isolable products, which decomposed readily, possessed an intact methoxyl group and carbamate ring at C9 but had suffered loss of the ester at C3.

These model studies suggested that, for maytansinoids, lithium borohydride initially acts as a base, abstracting the C9 carbinol hydrogen to open the carbinolamide ring system. This would also explain the formation of **6** in the reaction of maytanbutine **3**, since elimination of the C-3 ester is a facile process under mild base conditions.[1,8] The proposed mechanism would involve the formation of a C9 ketone intermediate, **11**,[9] that would also contain the



11

lithium carbamide salt on the β face of the molecule. Complexation of the borohydride reagent with the carbamide salt may be responsible for the stereospecificity of the subsequent reduction at C9.

The preparation of **4** and **6** provides the first examples of a maytansinoid with an irreversibly modified carbinolamide moiety. Previous work has demonstrated that two functional groups, the C3 ester and the C9 carbinolamide, are clearly required for a maytansinoid to show significant antileukemic activity.[4] Preliminary cytotoxicity studies have been carried out with **4** and show that **4** is much less cytotoxic than maytanbutine (**3**). In these studies, **1**, **3**, **4**, **5**, and **8** were screened against cell cultures of the P-815 leukemia and Lewis Lung carcinoma. Maytansinoids **1** and **3**, as expected, were the most active in these assays (ED_{50}s of ca. 10^{-6} μg/mL), **8** was slightly less active (ED_{50} = 10^{-5} μg/mL), and **4** and **5**, which is considered inactive, demonstrated similar cytotoxicities (ED_{50}s ca. 10^{-3} μg/mL). This preliminary data implies that the carbinolamide is involved in an alkylation reaction rather than simply an electrostatic interaction with a nucleophilic moiety in the cell. Further studies of this hypothesis are in progress.

Experimental Section

General Procedures. Melting points are uncorrected. Routine ^{1}H NMR and ^{13}C NMR spectra were recorded at 90 and 22.5 MHz. High-resolution ^{1}H NMR and two-dimensional ^{1}H COSY spectra were recorded at 270 MHz. All thin-layer chromatography was carried out on precoated plates (silica gel 60 F-254, EM Labs). Biological assays were performed in the Cell Culture Laboratory of the Department of Biology at VCU under the direction of Dr. Stanley Webb.

Maytancarbutine (4). A solution of maytanbutine (**3**) (51.9 mg, 0.0722 mmol) in 30 mL of THF (freshly distilled from $LiAlH_4$)[10] was stirred under a nitrogen atmosphere at room temperature as a 1-equiv mixture of $LiBH_4$ (45 μL of a 2.0 M solution in THF) and $Li(Et)_3BH$ (15 μL of a 1.0 M solution in THF) was added dropwise via syringe. The reaction mixture was allowed to equilibrate for 48 h while an additional 8.8 equiv of the borohydride mixture was added. The formation of product was monitored by TLC. The reaction was quenched by adding 1 mL of aqueous NH_4Cl. The mixture was then diluted with 50 mL of ethyl acetate and washed with 3 × 50 mL of aqueous NH_4Cl which was backwashed with 2 × 50 mL dichloromethane. All organic layers were combined, dried (Na_2SO_4), and evaporated to a white solid (56.7 mg). PTLC of this material on silica gel 60 developed with 5% methanol in dichloromethane afforded

(8) Suchocki, J. A.; Sneden, A. T. *J. Pharm. Sci.* **1987**, *76*, 738.
(9) A maytanside ester containing a ketone moiety at C9 has been tentatively identified as a minor product of the otherwise unproductive reaction of lithium triethylborohydride with maytanbutine **3**.
(10) For a warning regarding this method of purifying THF, see *Org. Synth.* **1973**, *5*, 976.

maytancarbutine (4) (32.2 mg, 66%) as a white crystalline solid: mp 159-162 °C; IR ($CDCl_3$) 3560, 3515, 3425, 2960, 1740, 1660 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (s, 3 H, C-4 CH_3), 1.02 (d, J = 7 Hz, 3 H, C-4′ CH_3), 1.11 (d, J = 6 Hz, 3 H, C-6 CH_3), 1.12 (d, J = 7 Hz, 3 H, C-4′ CH_3), 1.13 (m, 1 H, C-8 H_β), 1.16 (m, 1 H, C-8 H_α), 1.37 (d, J = 6 Hz, 3 H, C-2′ CH_3), 1.43 (m, C-6 H), 1.63 (s, 3 H, C-14 CH_3), 2.17 (dd, $J_{2,2}$ = 14, $J_{2,3}$ = 3 Hz, C-2 H_β), 2.61 (dd, $J_{2,2}$ = 14, $J_{2,3}$ = 12 Hz, C-2 H_α), 2.78 (m, 1 H, C-4′ H), 2.83 (s, 0.5 H), and 2.88 (s, 2.5 H) (C-2′NCH_3), 3.05 (d, $J_{5,6}$ = 9 Hz, 1 H, C-5 H), 3.05 (d, $J_{15,15}$ = 13 Hz, 1 H, C-15 H), 3.10 (s, 1 H, C-9 OH), 3.18 (s, 3.0 H) (C-1 NCH_3), 3.29 (s, 3 H, C-10 OCH_3), 3.40 (dd, $J_{9,10}$ = 2, $J_{10,11}$ = 9 Hz, 1 H, C-10 H), 3.73 (d, $J_{15,15}$ = 13 Hz, 1 H, C-15 H), 3.85 (br d, $J_{8\alpha,9}$ = 10 $J_{9,10}$ < 2 Hz, 1 H, C-9 H), 3.98 (s, 3 H, C-20 OCH_3), 4.72 (dd, $J_{2,3}$ = 12, 3 Hz, C-3 H), 4.80 (m, 1 H, C-7 H), 4.90 (br s, 1 H, C-7 $OCONH_2$), 5.61 (q, J = 7 Hz, 1 H, C-2′ H), 5.81 (dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, 1 H, C-11 H), 6.32 (dd, $J_{11,12}$ = 15, $J_{12,13}$ = 11, 1 H, C-12 H), 6.87 (d, $J_{12,13}$ = 11 Hz, 1 H, C-13 H), 6.72, 6.82 (d, $J_{17,21}$ = 1.5 Hz, 2 H, C-17 H, C-21 H); FABMS, m/z 722 (M + H); high-resolution EIMS, m/z 678.3264 ($C_{35}H_{51}ClN_2O_9$ = 678.3283) [M^+ - 43 (HNCO)], 505.2155 ($C_{27}H_{36}ClNO_6$ = 505.2212) [M^+ - 156 (side chain)], 490.2107 ($C_{26}H_{33}ClNO_6$ = 490.1996) [505 - CH_3], 487.2163 ($C_{27}H_{34}ClNO_5$ = 487.2125) [505 - H_2O].

Anal. Calcd for $C_{36}H_{52}ClN_3O_{10}$: C, 59.83; H, 7.20; N, 5.82. Found: C, 58.37; H, 7.20; N, 5.43.

Maycarsine (6). Maysine (5) (19.2 mg, 0.0350 mmol) was subjected to the same reaction conditions and work-up procedures as maytanbutine (3) to give a yellow solid. PTLC of this material on silica gel 60 developed with 5% methanol in dichloromethane afforded maycarsine (6) (6.0 mg, 32%) as a white crystalline solid: mp 131-133 °C; IR (KBr) 3420, 2930, 1720, 1667, 1340, 1080 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.07 (s, 3 H, C-4 CH_3), 1.15 (d, J = 7 Hz, 3 H, C-6 CH_3), 1.23 (m, 1 H, C-8 H_β), 1.34 (m, 1 H, C-8 H_α), 1.60 (m, 1 H, C-6 H), 1.70 (s, 3 H, C-14 CH_3), 2.72 (d, $J_{5,6}$ = 10 Hz, 1 H, C-5 H), 3.08 (d, $J_{15,15}$ = 12 Hz, 1 H, C-15 H), 3.27 (s, 3 H, C-1 NCH_3), 3.29 (s, 3 H, C-10 OCH_3), 3.39 (dd, $J_{9,10}$ = 2, $J_{10,11}$ = 10 Hz, C-10 H), 3.47 (d, $J_{15,15}$ = 12 Hz, 1 H, C-15 H), 3.89 (br d, $J_{8\alpha,9}$ = 10 Hz, C-9 H), 3.99 (s, 3 H, C-20 OCH_3), 4.76 (br s, 2 H, C-7 $OCONH_2$), 4.86 (dd, $J_{6,7}$ = 11 Hz, $J_{7,8\beta}$ = 11 Hz, C-7 H), 5.72 (dd, $J_{10,11}$ = 10, $J_{11,12}$ = 15 Hz, 1 H, C-11 H), 5.75 (d, $J_{2,3}$ = 15 Hz, 1 H, C-2 H), 6.10 (d, $J_{12,13}$ = 11 Hz, 1 H, C-13 H), 6.30 (dd, $J_{11,12}$ = 15, $J_{12,13}$ = 11, 1 H, C-12 H), 6.43 (d, $J_{2,3}$ = 15 Hz, 1 H, C-3 H), 6.72, 6.81 (d, $J_{17,21}$ = 1.5 Hz, 2 H, C-17 H, C-21 H), 3.20-3.45 (1 H, C-9 OH); FABMS, m/z 549 (M^+ + H); high-resolution EIMS, m/z 505.2145 ($C_{27}H_{36}ClNO_6$ = 505.2242 [M^+ - HNCO].

Reduction of 7. The aromatic carbinolamide 3,4-dihydro-4-hydroxy-2*H*-1,3-benzoxazin-2-one (7) (228 mg, 1.38 mmol) was subjected to the same reaction conditions described for 3 with the exception that only 1.1 equiv of the $LiBH_4/Li(Et)_3BH$ mixture was used. After workup, a yellow oil, which crystallized upon standing, was obtained. The crystals obtained were washed with diethyl ether to afford 9. PTLC of the mother liquor on silica gel developed with 7% methanol in dichloromethane afforded 9 and 10 as white crystalline solids. Compound 9 (112 mg, 66%) was spectroscopically identical with authentic samples of *o*-hydroxybenzyl alcohol. Compound 10 was spectroscopically determined to be 3,4-dihydro-2*H*-1,3-benzoxazin-2-one (35 mg, 17%): mp 193 °C; IR (KBr) 3278, 3170, 1724, 1185, 735 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.54 (s, 2 H), 6.32 (br s, 1 H), 6.99-7.26 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 42.7 (t), 116.8 (d), 125.8 (d), 128.1 (d), 151.6 (s).

9-*O*-Methylmaytanbutine (8). Maytanbutine (3) (114.1 mg, 0.1585 mmol) was dissolved in 50 mL of freshly distilled absolute methanol. A few crystals of *p*-toluenesulfonic acid were added, and the reaction mixture was allowed to equilibrate for 84 h. Solvent was evaporated in vacuo to give a murky solution, which was diluted with dichloromethane. Visible water was removed and the organic solvent was dried (Na_2SO_4) and evaporated to a solid, which was applied to column of silica gel and eluted with 1:2 diethyl ether-dichloromethane to afford white crystalline 9-*O*-methylmaytanbutine (8) (102.7 mg, 88%): mp 158-160 °C; IR (KBr) 3450, 2950, 1730, 1665, 1075 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.81 (s, 3 H, C-4 CH_3), 1.05 (d, J = 7 Hz, 3 H, C-4′ CH_3), 1.13 (d, J = 7 Hz, 3 H, C-4′ CH_3), 1.28 (d, J = 6 Hz, 3 H, C-6 CH_3), 1.32 (d, J = 6 Hz, 3 H, C-2′ CH_3), 1.63 (s, 3 H, C-14 CH_3), 2.20 (dd, $J_{2,2}$ = 14, $J_{2,3}$ = 3 Hz, C-2 H_β), 2.65 (dd, $J_{2,2}$ = 14, $J_{2,3}$ = 12 Hz, C-2 H_α), 2.80 (m, 1 H, C-4′ H), 2.82 (s, 0.5 H), 2.88 (s, 2.0 H), and 2.97 (s, 0.5 H) (C-2′NCH_3), 3.18 (s, 3 H, C-1 NCH_3), 3.28, 3.40 (2 s, 3 H ea, C-9 OCH_3, C-10 OCH_3), 3.50 (d, $J_{10,11}$ = 9 Hz, 1 H, C-10 H), 3.68 (d, $J_{15,15}$ = 13 Hz, 1 H, C-15 H), 3.98 (s, 3 H, C-20 OCH_3), 4.26 (m, 1 H, C-7 H), 4.75 (dd, $J_{2,3}$ = 12,3 Hz, C-3 H), 5.53 (q, J = 7 Hz, 1 H, C-2′ H), 5.68 (dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, 1 H, C-11 H), 6.39 (s, 1 H, C-9 NH), 6.43 (dd, $J_{11,12}$ = 15, $J_{12,13}$ = 11, 1 H, C-12 H) 6.74 (d, $J_{12,13}$ = 11 Hz, 1 H, C-13 H), 6.66, 6.82 (2 d, $J_{17,21}$ = 1.5 Hz, 1 H ea, C-17 H, C-21 H), 0.82-2.00 (3 H, C-6 H, C-8 H_2), 3.00-3.20 (2 H, C-5 H, C-15 H).

Reduction of 9-*O*-Methylmaytanbutine (8). 9-*O*-Methylmaytanbutine (8) (74.1 mg, 0.1011 mmol) was subjected to the same reaction conditions described for 3 with 11.0 equiv of the borohydride reagent. Workup followed by PTLC on silica gel 60 eluted with 5% methanol in dichloromethane afforded a major component which was found to be spectroscopically identical with the starting material (21.2 mg, 29%). A second major band (25.1 mg) was separated into two components by PTLC on alumina eluted with 2.5% methanol in dichloromethane. One component (9.0 mg) appeared to be 9-*O*-methylmaysine from its NMR spectrum: δ 0.83 (s, 3 H, C-4 CH_3), 1.28 (d, J = 5 Hz, 3 H, C-6 CH_3), 1.68 (s, 3 H, C-14 CH_3), 3.19 (s, 3 H, C-1 NCH_3), 3.28, 3.40 (2 s, 3 H ea, C-9 OCH_3, C-10 OCH_3), 3.98 (s, 3 H, C-20 OCH_3), 4.26 (m, 1 H, C-7 H), 5.54 (dd, $J_{10,11}$ = 9 Hz, $J_{11,12}$ = 10 Hz, C-11 H), 6.07-6.53 (m, 4 H, C-2 H, C-3 H, C-11 H, C-12 H), 6.81 (s, 1 H, C-9 NH), 6.94, 7.03 (2 d, 1 H ea, $J_{17,21}$ = 1.5 Hz, C-17 H, C-21 H). The other component (10.5 mg) decomposed in solution but did not show any resonances due to the C-3 ester in the NMR. The shifts of the C-7 H (δ 4.1), C-9 NH (δ 6.00), and C-9 OCH_3 (δ 3.34) indicated that the carbinol amide system was intact. No components were isolated that corresponded to maytancarbutine (4) or maycarsine (6).

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Electroorganic Chemistry. 113. Synthesis of (+)- and (-)-*N*-Methylpseudoconhydrine from L-Lysine Using Anodic Oxidation as the Key Reaction

Tatsuya Shono,* Yoshihiro Matsumura, Osamu Onomura, and Masaaki Sato

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan

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Synthesis of optically active piperidine alkaloids from L-lysine is particularly interesting since the piperidine skeleton found in some natural piperidine alkaloids has been known to be formed from L-lysine.[1]

As we have already reported, the anodic transformation of L-lysine to optically active pipecolinic acid is an excellent method of synthesis of piperidine skeleton from L-lysine.[2] Our previously reported enantioselective synthesis of (+)-*N*-methylconiine (5) from L-lysine was a typical example of applying this anodic transformation as the key reaction.[3,4] We report herein a first synthesis of optically

(1) Herbert, R. B. In *Rodd's Chemistry of Carbon Compounds*; Coffey, S., Ed.; Elsevier: Amsterdam, 1980; p 312.
(2) Shono, T.; Matsumura, Y.; Inoue, K. *J. Chem. Soc., Chem. Commun.* **1983**, 1169.

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