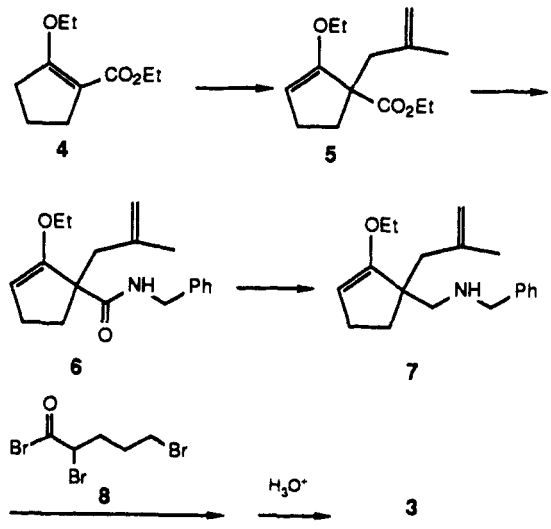
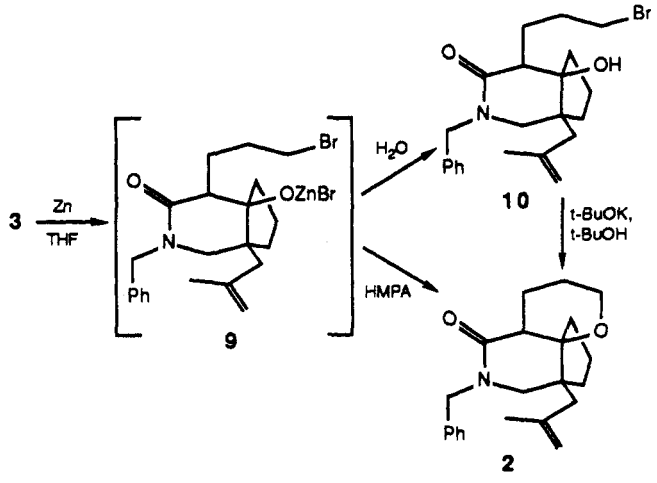
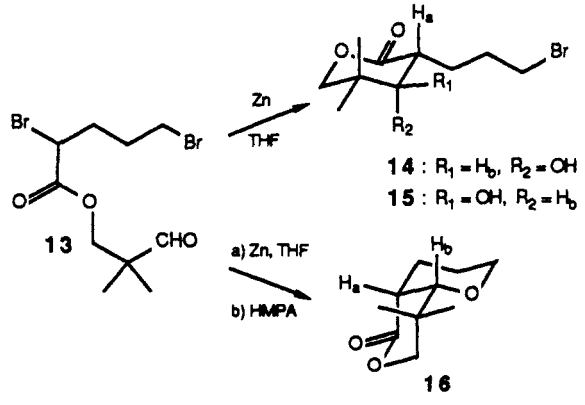
Scheme I



Scheme II



Scheme III



followed by oxidation of the resulting monoester with pyridinium dichromate in CH_2Cl_2 (62%). As shown in Scheme III, treatment of **13** with activated zinc in THF affords two β-hydroxy lactones, **14** and **15**, in a ratio of 6:1 and a total yield of 55%. The stereostructures of these materials were assigned on the basis of the observed H_a–H_b coupling constants, 3.4 Hz for **14** and 9.2 Hz for **15**. When the Reformatsky reaction is carried out in an identical manner, 4 equiv of HMPA is added, and the reaction kept at room temperature for 2 h before workup, lactone ether **16** (mp 80–81 °C) is obtained in 58% yield, along with 12% of an equimolar mixture of **14** and **15**. The structure of **16** derives from the H_a–H_b coupling constant of 2.6 Hz.

A final point to note is that our results with **13** show that the aldolate corresponding to **14** undergoes the intramolecular alkylation reaction substantially faster than does the aldolate corresponding to **15**. Further experiments to define the scope of the intramolecular Reformatsky reaction and its utility in the synthesis of polycyclic systems are underway.

Acknowledgment. This work was supported by a research grant from National Science Foundation, CHE-8418437.

Supplementary Material Available: Synthetic procedure used to convert amide **3** into lactam **2** and complete spectral data for compounds **2**, **3**, **5**–**8**, and **11**–**16** (5 pages). Ordering information is given on any current masthead page.

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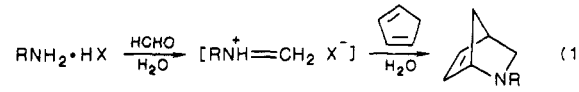
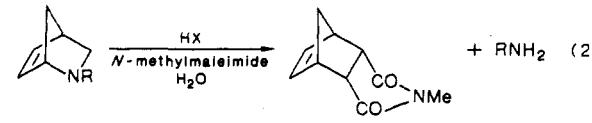
Immonium Ion Based Synthetic Methodology: A Novel Method for the N-Methylation of Dipeptides and Amino Acid Derivatives via Retro Aza Diels–Alder Reactions

Summary: A novel method for the N-methylation of amino acid derivatives and dipeptides is detailed that features facile room-temperature retro Diels–Alder reactions of N-substituted 2-azanorbornenes with trapping of the incipient immonium ion with triethylsilane/trifluoroacetic acid.

Sir: It has been shown that immonium ions generated in situ from primary alkylamines, acid, and aqueous formaldehyde in water undergo a facile cyclocondensation with cyclopentadiene at room temperature (cf. eq 1).[1] More



recently we have demonstrated that 2-azanorbornenes undergo smooth acid-catalyzed heterocycloreversion in water at ambient temperature in the presence of *N*-methylmaleimide (cf. eq 2).[2] It occurred to us that the

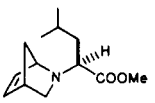
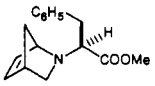
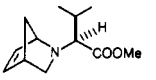
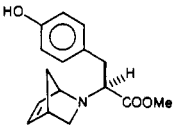
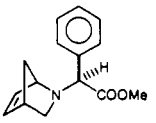
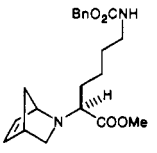
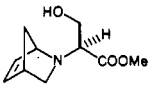
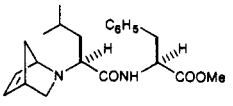
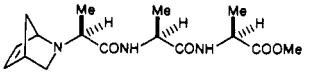


extremely mild reaction conditions employed in eq 1 and 2 coupled with the compatibility of the chemistry illustrated with functional groups would permit access to N-methylated amino acid derivatives and small peptides provided the immonium ion species generated during the

(1) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.
(2) Grieco, P. A.; Parker, D. T.; Fobare, W. F.; Ruckle, R. *J. Am. Chem. Soc.* **1987**, *109*, 5859.

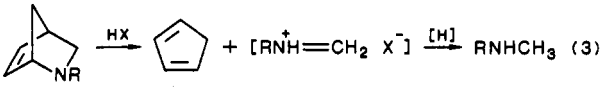
0022-3263/87/1952-5746$01.50/0

Table I. Reaction of Immonium Ions Derived from Amino Acid Derivatives and Peptides with Cyclopentadiene[a]

entry	substrate	time	product	ratio of diastereomers	% yield[b]
1	H-Leu-OMe·HCl	45 min		1.7:1	94
2	H-Phe-OMe·HCl	45 min		1.8:1	84
3	H-Val-OMe·HCl	2 h		4.0:1	82
4	H-Tyr-OMe·HCl	1 h		2:1	87
5	L-phenylglycine methyl ester·HCl	30 min		1.7:1	94
6	H-Lys(Z)-OMe·HCl	45 min		1.1:1	98
7	H-Ser-OMe·HCl	1 h		3.3:1	98
8	H-Leu-Phe-OMe·HCl[c]	2 h		1:1	87
9[d]	H-Ala-Ala-Ala-OMe·HOAc	1 h		1:1	81

[a] All reactions were run at ambient temperature with 1.0 equiv of amine hydrochloride, 1.7–8.0 equiv of 37% aqueous formaldehyde solution, and 3.0–8.0 equiv of cyclopentadiene unless otherwise stated. The resulting homogeneous aqueous solutions were ca. 1.0 M in amine hydrochloride. [b] Isolated yields. [c] H-Leu-Phe-OMe·HCl is only partially soluble in water at 1.0 M concentration; however, this is of no consequence to the success of the reaction. [d] Reaction was conducted on the acetic acid salt which is commercially available.

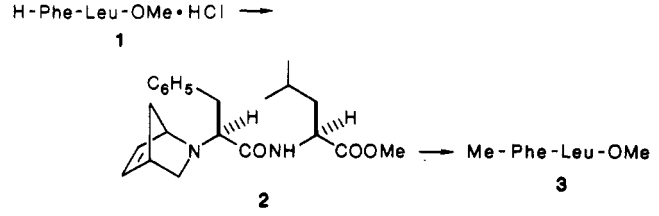
retro aza Diels–Alder process could be trapped by reduction (cf. eq 3).[3] The success of any N-methylation pro-



(3)

cedure would be critically dependent upon the extent of racemization. We detail below a general, two-step procedure for the N-methylation of amino acid derivatives and small peptides which, within the limits of detection, proceeds without racemization.

The general process is illustrated below for the preparation of *N*-methyl-L-phenylalanyl-L-leucine methyl ester (**3**). Exposure of a 1.5 M aqueous solution of the hydrochloride salt **1** of L-phenylalanyl-L-leucine methyl ester to 5.0 equiv of cyclopentadiene and 3.0 equiv of 37% aqueous



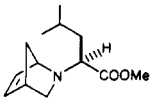
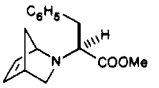
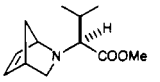
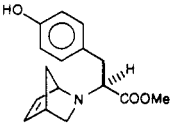
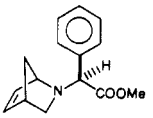
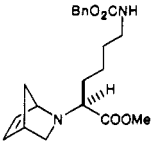
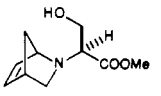
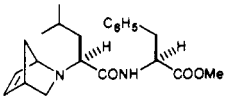
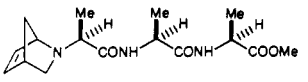
formaldehyde provides after 2 h at ambient temperature a 95% yield of the 2-azanorbornene derivative **2** as a 1:1 mixture of diastereomers.[4] Subsequent treatment of a 0.1 M solution of azanorbornene **2** in chloroform/trifluoroacetic acid (1:1) with 3.0 equiv of triethylsilane provides after 20 h at room temperature an 84% yield of *N*-methyl-L-phenylalanyl-L-leucine methyl ester (**3**), $[\alpha]_D^{28}$ −67.2° (*c* 1.4, $CHCl_3$). Any racemization that may accompany the retro aza Diels–Alder process is less than the detection limit (0.06–0.07%) using proton NMR.[5]

(3) For recent developments in the N-methylation of amino acid derivatives, see: (a) O'Donnell, M. J.; Bruder, W. A.; Daugherty, B. W.; Liu, D.; Wojciechowski, K. *Tetrahedron Lett.* **1984**, *25*, 3651. (b) Freidinger, R. M.; Hinkle, J. S.; Perlow, D. S.; Arison, B. H. *J. Org. Chem.* **1983**, *48*, 77. (c) Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 65. (d) Shuman, R. T.; Smithwick, E. L.; Smiley, D. L.; Brooke, G. S.; Gesellchen, P. D. *Peptides: Structure and Function, Proc. 8th Amer. Pept. Symp.* **1983**, 143. (e) Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906. (f) Olsen, R. K. *J. Org. Chem.* **1970**, *35*, 1912.

(4) The diastereomers can be readily separated by column chromatography. Proton NMR analysis of each diastereomer reveals, within the limits of detection, no racemization.[5]

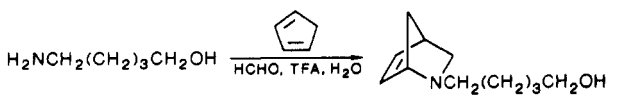
(5) (a) Dewey, R. S.; Schoenewaldt, E. F.; Joshua, H.; Paleveda, W. J.; Schwam, H.; Barkemeyer, H.; Arison, B. H.; Veber, D. F.; Denkewalter, R. G.; Hirschmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 3254. (b) Halpern, B.; Nitecki, D. E.; Weinstein, B. *Tetrahedron Lett.* **1967**, 3075.

Table II. Preparation of N-Methylated Amino Acid Derivatives and Peptides via a Retro Aza Diels–Alder Reaction[a]

entry	substrate	product[b]	$[\alpha]_D$,[c] deg	% yield[d]
1		Me-Leu-OMe·TFA	+25.2	91
2		Me-Phe-OMe	+28.6	92
3		Me-Val-OMe·TFA	+27.6	78
4		Me-Tyr-OMe	+35.4[e]	75
5		*N*-methylphenylglycine methyl ester	+131.3	88
6		Me-Lys(Z)-OMe	+2.0	76
7		Me-Ser-OMe-TFA	−7.4[f]	83
8		Me-Leu-Phe-OMe	+13.4	78
9		Me-Ala-Ala-Ala-OMe	−70.4	67

[a] All reactions were conducted at room temperature for 20 h in chloroform/trifluoroacetic acid (1:1), 3.0 equiv of triethylsilane. The TFA/$CHCl_3$ solution was 0.1 M in azanorbornene. [b] Derivatives were isolated as TFA salts for convenience, since in these cases the free bases were exceedingly water soluble or volatile at reduced pressures. [c] All rotations were recorded in chloroform at 28 °C unless noted otherwise. [d] Isolated yields. [e] Rotation recorded in ETOH [lit.[9] $[\alpha]_D$ +34.5° (*c* 1.6, EtOH)]. [f] Rotation recorded in acetone.

The two-step sequence illustrated in eq 1 and 3 is applicable to a number of other amino acid derivatives and small peptides (see Tables I and II). As indicated in Table I, the formation of the azanorbornene adducts proceeds smoothly at ambient temperature in 0.5–2.0 h and, more importantly, is compatible with unprotected phenols and hydroxyls (Table I, entries 4 and 7). In general, amino alcohols need no protection. For example, treatment of a 1.0 M solution of 5-amino-1-pentanol with 1.0 equiv of TFA, 1.2 equiv of 37% aqueous formaldehyde, and 4.0 equiv of cyclopentadiene provides after 1 h a 95% yield of 2-azanorbornene 4.[6] The aza Diels–Alder reaction is



4

not effected by sterically encumbered amino acid derivatives (Table I, entries 3 and 5). Most significant is the fact that no racemization accompanies the formation of the azanorbornene adducts.

With respect to the second step of this two-step process, heterocycloreversion proceeds smoothly at room temperature in the presence of trifluoroacetic acid, which catalyzes the retro Diels–Alder reaction. The success of this N-methylation sequence is made possible by (1) the efficient trapping of the released immonium ion species by the triethylsilane/trifluoroacetic acid system[7] and (2) the absence of any racemization. Of particular interest, in this regard, is the case of phenylglycine (Table II, entry 5), which is known to undergo extremely facile racemization. The optical purity of the *N*-methylphenylglycine methyl ester obtained was established by proton NMR in the presence of the chiral shift reagent tris[3-[(heptafluoro-

(6) This experiment was carried out by Heidi Berven, Indiana University.

(7) *N*-Acyl immonium ions have previously been reduced by employing the triethylsilane/trifluoroacetic acid system. [Auerbach, J.; Zamore, M.; Weinreb, S. *J. Org. Chem.* **1976**, *41*, 725. Also see ref 3b.]

propyl)hydroxymethylene]-(+)-camphorato]europium-(III).[8] No racemization was detected.

The N-methylation sequence is also applicable to unprotected amino acids. For example, exposure of a 1.5 M aqueous solution of L-leucine to 1.0 equiv of 37% aqueous formaldehyde solution and 2.3 equiv of cyclopentadiene for 5 h at ambient temperature followed by treatment of the crude Diels–Alder adduct (0.1 M in $CHCl_3$/TFA, 1:1) with 3.0 equiv of triethylsilane at room temperature for 15 h provided upon workup a 70% yield of *N*-methyl-L-leucine.

The immonium ion generated during the course of the heterocycloreversion process (eq 3) can also be reduced by employing sodium cyanoborohydride. For example, treatment of a 0.02 M solution of azanorbornene **2** as its trifluoroacetate salt in methanol with 20 equiv of sodium cyanoborohydride provides after 8 h at ambient temperature an 81% yield of *N*-methyl-L-phenylalanyl-L-leucine methyl ester (**3**). No racemization is observed if trifluoroacetic acid is added as required during the course of the reaction to maintain the pH of 3.5–4.0.

The general N-methylation sequence detailed above should be of considerable use in peptide synthesis. The uniqueness of this new method is that both transformations are conducted in acidic medium, thus avoiding complications due to base-sensitive protecting groups and racemization.[10,11]

Acknowledgment. This investigation was supported in part by a grant from the National Science Foundation. The 300-MHz NMR instrument (Varian XL-300) used in the above studies was purchased with funds provided by the National Institutes of Health (Grant RR-1882).

(8) Employing DL-*N*-methylphenylglycine methyl ester, enantiomeric separations at 300 MHz in $CDCl_3$ of ca. 103 Hz were realized in the presence of 0.8 molar equiv of lanthanide shift reagent.

(9) Huguenin, R. L.; Boissonnas, R. A. *Helv. Chim. Acta* **1961**, *44*, 213.

(10) All new compounds have been fully characterized by IR, NMR, $[\alpha]_D$, and MS and/or combustion analysis.

(11) The following experimental employing H-Tyr-OMe·HCl serves as a general procedure for the two-step N-methylation sequence. To a homogeneous solution of H-Tyr-OMe·HCl (638 mg, 2.7 mmol) in 1.8 mL of water were added with vigorous stirring cyclopentadiene (0.50 mL, 6.1 mmol) and an aqueous solution of 37% formaldehyde (0.24 mL, 3.0 mmol). After 1 h at ambient temperature, the heterogeneous reaction mixture was washed with hexane and neutralized with 5% sodium bicarbonate solution. The product was isolated by extraction with methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel. Elution with methylene chloride/methanol/ammonium hydroxide, 96:3:1, provided 654 mg (87%) of a diastereomeric mixture (2:1) of 2-azanorbornenes, which were used directly in the next reaction. To a solution of a portion of the above 2-azanorbornene adducts (311 mg, 1.14 mmol) in 5.7 mL of chloroform was added 5.7 mL of trifluoroacetic acid and triethylsilane (0.55 mL, 3.42 mmol). The resulting homogeneous reaction mixture was stirred at ambient temperature under argon. After 20 h the solvent was removed under reduced pressure. The crude yellow product was dissolved in 2.0 mL of chloroform, treated with 4.0 mL of 10% hydrochloric acid, and washed with hexane/ether, 1:1. The aqueous layer was neutralized with 5% sodium bicarbonate solution and the product was isolated by extraction with methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded 219 mg (82%) of Me-Tyr-OMe as an oil. Purification of the product by flash chromatography on silica gel employing chloroform/methanol/ammonium hydroxide, 96:3:1, provided after recrystallization from methylene chloride 179 mg (75%) of Me-Tyr-OMe: mp 109–111 °C; $[\alpha]_D$ +35.4° (*c* 1.08, EtOH) [lit.[9] mp 109–111 °C; $[\alpha]_D$ +34.5° (*c* 1.6, EtOH)].

(12) Recipient of a Predoctoral Fellowship from La Universidad de Los Andes, Merida, Venezuela.

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Received August 4, 1987

Additions and Corrections

Vol. 49, 1984

Richard E. Moore,* Adrian J. Blackman, Chad E. Cheuk, Jon S. Mynderse, Gayle K. Matsumoto, Jon Clardy, Ronald W. Woodard, and J. Cymerman Craig. Absolute Stereochemistries of the Aplysiatoxins and Oscillatoxin A.

Page 2489. The identities of O10 and C31 should be reversed in the X-ray drawing in Figure 2.