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The Stereocontrolled Synthesis of Enantiopure α-Methano Heterocycles and Constrained Amino Acid Analogs

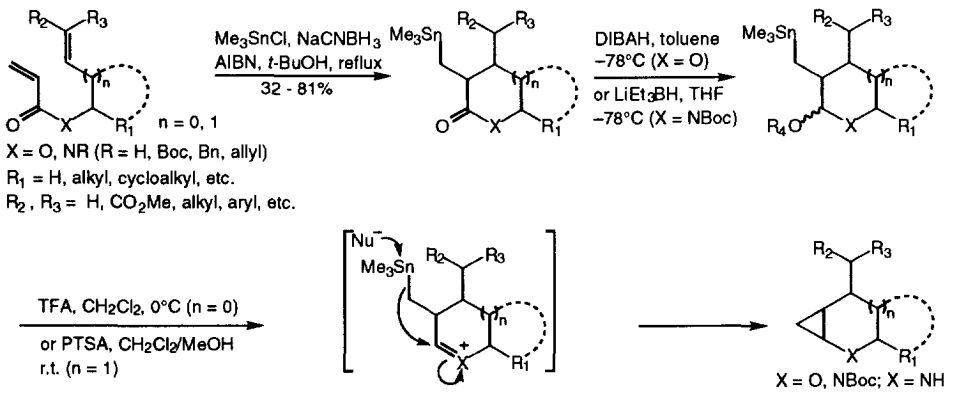
Stephen Hanessian,* Ulrich Reinhold and Sacha Ninkovic

Department of Chemistry, Université de Montréal, P.O.Box 6128, Station Centre-ville, Montréal, Québec H3C 3J7, CANADA

Abstract: *Addition of trimethylstannyl radicals to acrylate and acrylamide derivatives that contain olefinic groups leads to the corresponding lactones and lactams with good to excellent stereochemical control. α-Methano heterocycles can be easily elaborated from the α-trimethylstannylmethyl intermediates via putative oxonium and iminium ions generated under acids conditions.*

The synthesis of conformationally constrained amino acids and related molecules has gained enormous popularity in the context of peptidomimetic research and the quest for novel mechanism-based drug design.[1] In 1992, we reported on an expedient and unprecedented free-radical addition-carbocyclization of terminal dienes induced by trimethylstannyl radicals leading to tetrahydrofurans, pyrrolidines and related heterocycles, as well as to carbocyclic compounds.[2,3] A novel oxidative cleavage of the C-Sn bond with ceric ammonium nitrate was also discovered in the course of the study. We now report on the application of this methodology to the stereocontrolled synthesis of lactones and lactams. We also disclose a new and general route to enantiomerically pure α-methano bicyclic and tricyclic heterocycles by solvolytic cleavage of α-trimethylstannylmethyl oxonium and iminium ions generated under acidic conditions (Scheme 1).

Scheme 1



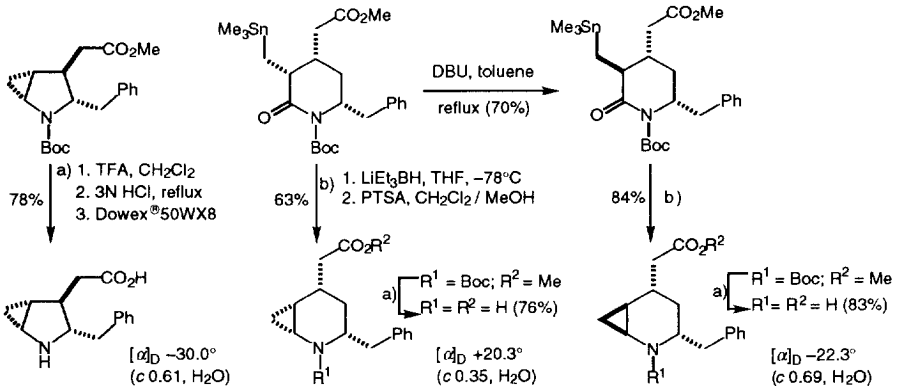
The method involves the addition of trimethylstannyl radicals to acrylates and acrylamide derivatives that contain a suitably situated acceptor olefinic extremity. In general, the cyclizations were reasonably effective in spite of the intermediacy of resonance stabilized trimethylstannyl propionyl α-radicals.[4,5] Table 1 lists a number of di- and trisubstituted lactones and lactams prepared in yields ranging from 32-81%.[6] The newly formed bond included vicinal substituents at C2/C3 in all of the five-membered ring heterocycles with

an *anti* (*trans*) disposition in the major isomers (Table 1, entries 1-9, 11). It is of interest that the amide nitrogen atom can be unsubstituted, or protected as an N-Boc, N-benzyl or even an N-allyl group (Table 1, entries 3-5). The N-allylamide led to the product arising from the initial attack of the trimethylstannyl radical onto the acryloyl group exclusively (Table 1, entry 5).[7] The effect of resident chirality that is vicinal to the acceptor end of the dienic system was also studied. Thus, the product elaborated upon from *L*-phenylalanine gave the *anti/anti* isomer as the major product (Table 1, entry 9). The homologated analog shown in entry 10, led to the *syn/syn* isomer in preponderance. Stereochemical assignments were ascertained from n.O.e. studies and single crystal X-ray diffraction analysis. Carbocyclizations to bicyclic lactams led to surprisingly good selectivities while maintaining efficiency (Table 1, entries 11, 12).

The C2/C3 *anti* stereochemical outcome of the carbocyclization reactions leading to the butyrolactone and pyrrolidinone analogs shown in Table 1 is different from analogous tetrahydrofurans and pyrrolidines, where the *syn* isomer was invariably favored.[2] Although the reasons for the reversal are not entirely clear, the *anti* stereochemistry may be the consequence of the geometry of the "radical-enolate",[4] the relative orientation of the other olefinic appendage, and the fact that the transition state of such stabilized radicals may be more product-like. The possibility of equilibration of an initially formed *syn* isomer under the reaction conditions cannot be excluded.

With an efficient access to stereochemically and functionally diverse α-trimethylstannylmethyl lactones and lactams in hand, we explored methodology that would lead to α-heteroatom substituted bicyclic and tricyclic cyclopropanes (Scheme 2).[6] We envisaged that the acid-catalyzed formation of oxonium or iminium ion intermediates would trigger spontaneous cyclization to the corresponding α-methano products by loss of the trimethylstannyl group as shown in Scheme 2.[8,9]

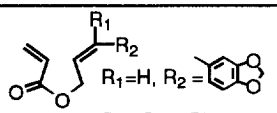
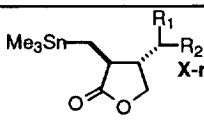
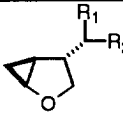
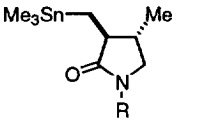
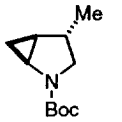
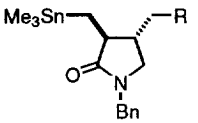
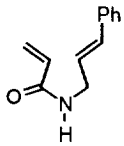
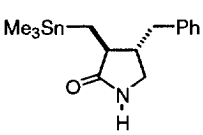
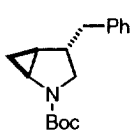
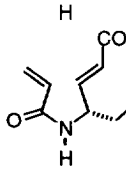
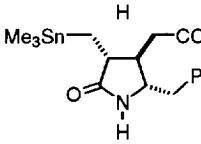
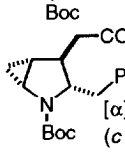
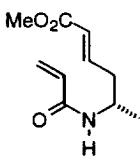
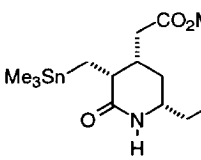
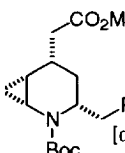
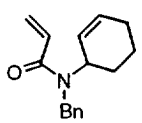
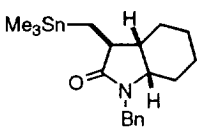
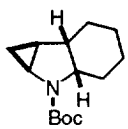
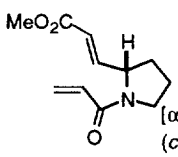
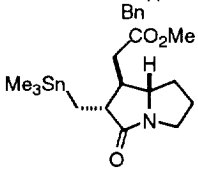
Scheme 2



Reduction[10] of the lactone and the lactam derivatives followed by acid treatment of the corresponding hemiacetals and hemiaminals respectively led to the expected α-methano heterocycles in excellent yields (Table 1, entries 1-5, 8-11). The all-*syn* isomer (Table 1, entry 10) could be smoothly epimerized with DBU in refluxing toluene to afford the *syn-anti* diastereomer in 70% yield with recovery of starting material (16%) (Scheme 2). Treatment with PTSA in methanol/dichloromethane afforded the corresponding α-methano derivative. The N-Boc and ester groups were cleaved under standard conditions to afford the corresponding α-methano bicyclic amino acids as pure diastereomers .

The novel α-methano heterocycles reported in this paper can be considered to be rigid mimics of ω-amino acids such as GABA and its congeners, with potentially interesting CNS-related agonist or antagonist activity.[11] On the other hand, when deployed with an appropriate DNA-binding motif or an intercalating

Table 1. Diastereoselective Synthesis of Lactones, Lactams and α-Methano Heterocycles

Entry	Diene	Major Lactone, Lactam	Yield[a,b]	Method[c]	α-Methano derivative Yield[a,b,d]
1	 R_1=H, R_2=	 X-ray	53% (4:1)[e]	A	 85%[f]
2	$R_1 = R_2$ = Ph		66% (14:1)	A	94% (14:1)
3	R = Bn		58% (4.3:1)[g]	B	 82%[f]
4	R = Boc		32% (7:1)	B	
5	R = allyl		64% (5:1)	A	
6	R = CO_2Me		80% (4:1)	A	
7	R = Ph		81% (4:1)	B	–
8			57% (4.5:1)[g]	B	 81%[f]
9	 $[\alpha]_D$ −23.1° (*c* 0.60, $CHCl_3$)		64% (5.5:1)[g]	B	 65%[f, h] $[\alpha]_D$ +58.6° (*c* 0.75, $CHCl_3$)
10	 $[\alpha]_D$ −26.1° (*c* 1.05, $CHCl_3$)		60% (4.5:1)[g,i]	B	 63%[f] $[\alpha]_D$ +27.1° (*c* 0.59, $CHCl_3$)
11			74% (>10:1)[g]	A	 86%[f]
12	 $[\alpha]_D$ −82.1° (*c* 0.9, $CHCl_3$)		63% (5.5:1)	A	–

a. Isolated product. b. Diastereomer ratio by ^1H, ^{13}C NMR. c. Method **A**, **B**, see ref. 6. d. Cyclopropanation method, see ref. 6. e. Major isomer isolated by fractional crystallization from MeOH . f. Single diastereomer. g. For transformation into the N-Boc protected lactams see ref. 6; N-Boc products of entry 3, 8 and 10 are separable by column chromatography. h. Diastereomers separable by flash column chromatography. i. X-ray structure of corresponding racemic 6-phenyl lactam analog.

agent on the heterocycle, these α-methano analogs could act as potential DNA bioalkylation agents by virtue of the generation of onium species and their reaction with specific purine or pyrimidine bases.[12]

Further studies aimed at the synthesis of α-methano heterocycles as rigid analogs of amino acids with demonstrated CNS functions, and base-specific DNA modifiers are in progress.

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6. *Methods of radical cyclization.* Method **A**: Diene, Me_3SnCl , $NaCNBH_3$ and AIBN (cat.) are heated in refluxing *t*-BuOH (see ref. 2). Method **B**: A solution of 1.5-4.0 eq. $NaCNBH_3$ and AIBN (cat.) in MeOH is added slowly (1 to 13 h) to a solution of diene and 1.1 - 1.3 eq. Me_3SnCl in refluxing *t*-BuOH using a syringe pump.

   Method of cyclopropanation: Lactones are reduced to the corresponding lactols with Dibal in toluene at –78°C; the N-Boc protected lactams are reduced with $LiEt_3BH$ in THF at –78°C (see ref. 10). The lactols and the N,O-hemiaminals are then treated with 12 eq. TFA in CH_2Cl_2 (0.05M) at 0°C to give the cyclopropane derivatives. For entry 10, 3 eq. of PTSA in a 1:1 mixture of CH_2Cl_2/MeOH (0.02M) at r.t was used. In entry 1, the lactol was treated first with *i*-PrOH under acid catalysis (PPTS) to form the corresponding acetal in 82% yield.

   N-Boc protection of lactam: The deprotection of N-Bn protected lactams was performed by reductive cleavage with Li/NH_3. The N-Boc protection was carried out with Boc_2O, DMAP and Et_3N in CH_2Cl_2 (78%, 96%, 96% , 97%, 71% and 28 % starting material for entry 3, 7-9 and 11) or in CH_3CN (90% for entry 10). The diastereomers of the Boc-protected lactams (entry 3, 8 and 10) are separable by column chromatography.
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