ORGANIC LETTERS

2003
Vol. 5, No. 23
4341−4344

A Flexible Approach to (*S*)-5-Alkyl Tetramic Acid Derivatives: Application to the Asymmetric Synthesis of (+)-Preussin and Protected (3*S*,4*S*)-AHPPA

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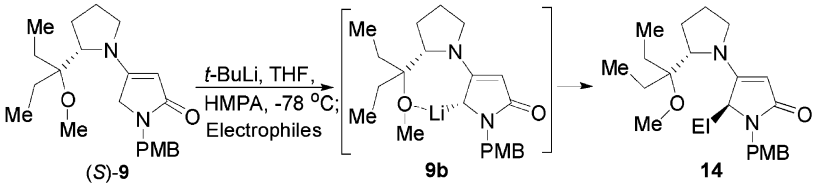
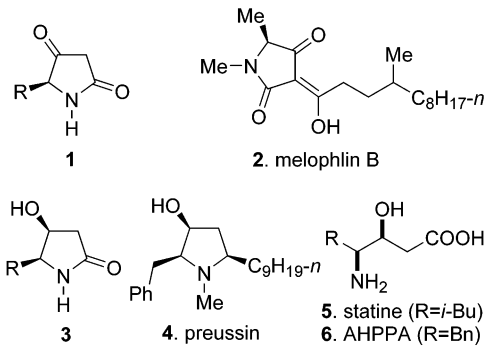
Received August 26, 2003

ABSTRACT



A flexible asymmetric approach to 5-alkyl tetramic acid derivatives is described, which is based on the use of 9 as the first synthetic equivalent to chiral nonracemic tetramic acid 5-carbanionic synthon 9b. The existence of the carbanion intermediate 9b was proven by trapping with trimethylchlorosilane. Application of the present method to the synthesis of antifungal alkaloid (+)-preussin, as well as protected (3*S*,4*S*)-AHPPA 6, is also described.

5-Alkyl tetramic acids **1** are the key structural features found in a number of natural products that display a range of biological properties.[1] For example, melophlin B **2** is a compound reversing the phenotype of ras-transformed cells and was isolated from the Indonesian marine sponge *Melophlus sarassinorum*.[2] Moreover, 5-alkyltetramic acids are ready precursors of 2-pyrrolidinones[3] **3**, which are valuable building blocks for another two classes of bioactive natural products, namely, pyrrolidine alkaloids such as preussin[4] **4** and β-hydroxy-γ-amino acids such as (3*S*,4*S*)-statine **5** and (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) **6**, which are important peptide mimetics.[5] Consequently, the synthesis of tetramic acids has attracted a great deal of interest.[1]



However, most of the known methods for the synthesis of tetramic acids use α-amino acids as the starting materials

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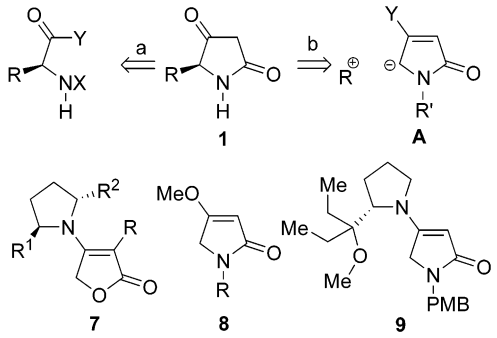
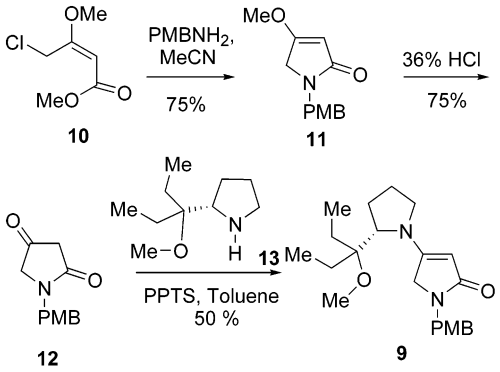
10.1021/ol035617a CCC: $25.00
Published on Web 10/24/2003

Scheme 1



Scheme 2



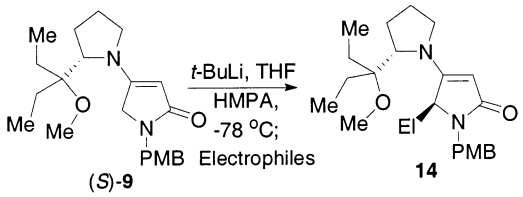
(Scheme 1, path a),[6] which although reliable has a lack of flexibility because the alkyl group presents in the C-5 position of tetramic acids comes from the side chain of the starting α-amino acid. A flexible approach to 5-substituted tetramic acids would be one that allows the introduction of the C-5 substituents in a flexible manner (Scheme 1, path b).

Although chiral tetronic acid derivative **7**[7−9] and nonchiral tetramate **8**[10,11] were reported 15 years ago as, respectively, the synthetic equivalents to the corresponding tetronic acid carbanionic synthon and tetramic acid synthon **A** and the latter is currently being applied to the synthesis of other natural products,[12] the chiral nonracemic tetramic acid synthon (*R* or *S*)-**A** remains unexploited. Inspired by the pioneering work of Schlessinger on the chemistry of tetronic acid **7**,[7] we now wish to report herein the development of compound (*S*)-**9** as the first synthetic equivalent to the chiral nonracemic tetramic acid 5-carbanionic synthon (*R* or *S*)-**A** and its use in the asymmetric synthesis of (+)-preussin **4** and protected (3*S*,4*S*)-AHPPA **6**.

The synthesis of the requisite chiral nonracemic synthon equivalent (*S*)-**9** is depicted in Scheme 2. Treatment of *p*-methoxybenzylamine with known methyl (*E*)-4-chloro-3-methoxy-2-butenoate **10**[13] gave tetramate **11** in 75% yield. Acidic hydrolysis of **11** afforded *N*-protected tetramic acid **12** in 75% yield. Heating a mixture of **12** and (*S*)-prolinol derivative **13**[14] in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) provided the desired chiral tetramic acid synthon equivalent **9** in 50% yield.

With access to quantities of synthon equivalent **9** secured, we then proceeded to study its deprotonation and subsequent reaction with electrophiles (Scheme 3). As a first test,

Scheme 3



compound **9** was deprotonated with 1.2 molar equiv of *tert*-butyllithium in THF (cosolvent HMPA, −78 °C, 1 h), and the anion formed was quenched with deuteriomethanol (MeOD, −78 °C, 20 min.), which yielded the C-5 deuterio product **14a** in 78% yield (Table 1, entry 1). Encouraged by this result, the anion generated from **9** (1.2 equiv *t*-BuLi, THF−HMPA 20:1, −78 °C, 1 h) was allowed to react with methyl iodide (−78 °C, 7 h), which afforded **14b** as the sole regioisomer and in 99% *de* (combined yield, 87%) (Table 1, entry 2).

The reaction of the lithiated **9** with other carbon electrophiles proceeded similarly (Table 1, entries 3−7) with excellent regio- and diastereoselectivities, which were ascertained by combining HPLC and ^{1}H NMR spectral analysis. In addition, on the basis of the comparison of the allylation product **14e** with an epimerized sample (in 55:45 ratio) by mean of HPLC analysis, the minor isomer appearing in the HPLC analysis was attributed to the diastereomer

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Table 1. Results for the Reaction between Lithiated **9** and Electrophiles

entry	electrophiles	products (yields, %)[a]	% *de*
1	MeOD	**14a** (78)	4[b]
2	MeI	**14b** (87)	99[c]
3	*n*-C_4H_9I	**14c** (71)	100[c]
4	*n*-$C_6H_{13}I$	**14d** (69)	100[c]
5	CH_2=$CHCH_2I$	**14e** (77)	97[c]
6	$BrCH_2CO_2Et$	**14f** (84)	98[c]
7	BnBr	**14g** (85)	100[c]
8	TMSCl	**14h** (45)	100[c]

[a] Isolated yields. [b] *de* determined by ^{1}H NMR. [c] *de* determined by HPLC analysis.

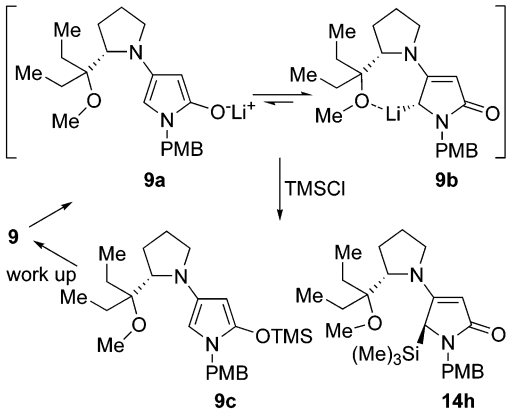
instead of regioisomer. It is noteworthy that, as indicated by ^{1}H and ^{13}C NMR spectra, alkylation products **14b**−**14d** exist, in each case, in only one rotamer in $CDCl_3$, whereas compounds **14e**−**h** exist as a rotameric mixture. The nature of the rotameric mixture was proven by the ultimate transformation of **14g** into (+)-preussin **4** (*vide infra*).

Compared with related systems (**7** and **8**), the high regio-, chemo-, and diastereoselectivities observed during the alkylation of (*S*)-**9** deserve comments. For the alkylation of the vinylogous enolates derived from 4-(2,5-substituted pyrrolidino)-2(5*H*)-furanones **7**, although excellent diastereoselectivities were obtained with the chiral auxiliary possessing a C_2 symmetry (**7**, $R_1 = R_2$ = Me or CH_2OMe),[7a,e−h,8] when using more cheap and easily available L-prolinol derivatives as the chiral auxiliaries,[7b,c,d,9] good diastereoselectivities could be obtained only in the cases where an alkyl group is presented at the C-2 position of **7** ($R \neq H$).[9] As regarding the chemo- and regioselectivities during the alkylation of the dienolates derived from tetramate **8**, when allyl halide or benzyl bromide was used as the alkylating agent, significant quantities of C-3 allylation product[12a] and 5,5-dibenzylation product[10b] were observed, respectively.

The different behavior of the anions derived from compounds **7**, **8**, and **9** might implicate that, in our case, among two possible lithiated intermediates **9a** and **9b**, the latter was the predominant structure. To test this hypothesis, trapping of the lithiated intermediates by trimethylchlorosilane was envisioned. Thus when the lithiated intermediates derived from **9** were treated with 2.5 molar equiv of trimethylchlorosilane, C-5 silylated product **14h** was isolated in 45% yield together with a 45% yield of the starting material (Table 1, entry 8). The recovery of **9** may due to the competing *O*-silylation of **9a**, which regenerated, during aqueous workup, the starting **9** (Scheme 4).

This result is significant in carbanionic chemistry,[15] since the selective *O*-silylation of enolates is a very general and routine chemoselective reaction, as the result of the formation of a strong O−Si bond. The exclusive *O*-silylation of the

Scheme 4



anions generated either from **7**[16] or **8**[10a] have also been reported. It is admitted that the isolated yield of **14h** (45%) could not reflect the real composition of the lithiated intermediates **9a**−**9b** in the reaction media, since more rapid *O*-silylation of the minor intermediate **9a** (comparing with *C*-silylation) will favor its formation from **9b**. On the basis of this consideration, the carbanionic intermediate **9b** should be predominant over **9a** in the reaction mixture.

Although the stereochemistry of the alkylation products **14** is unknown at this stage, on the basis of both the chelating intermediate **9b** and vinylogous enolate **9a**, it is reasonable to assume that the newly formed stereogenic center has *S*-configuration that resulted either from an inversion of configuration at C-5 of **9b** or from the approach of electrophiles from the *si* face of the vinylogous enolate **9a** avoiding the $A^{1,3}$-interaction.

To gain solid proof of the stereochemistry of the alkylated products **14** and to demonstrate the versatility of the present method, the asymmetric synthesis of (+)-preussin **4**,[17] a potent antifungal agent isolated from fermentation broths of both *Aspergillus ochraceus* and *Preussia* sp., was undertaken (Schemes 5 and 6).

Thus treatment of **14g** with a 10% HCl solution in THF for 26 h gave the corresponding crude tetramic acid **15**, which without further purification was treated at 0 °C with sodium borohydride in methanol,[3] to provide *cis*-**16**. The yield over two steps was 82%, and the *cis*/*trans* ratio was about 20:1, which was deduced from the following step.

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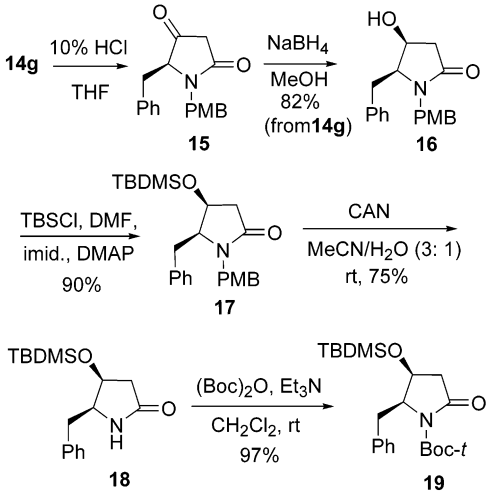
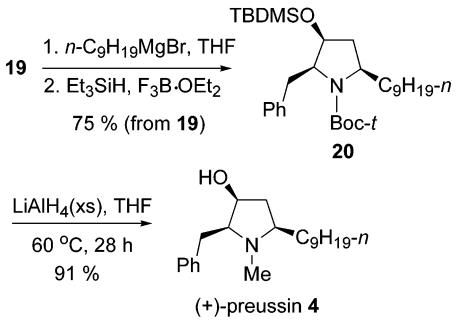
Scheme 5



O-Protection (TBDMSCl, imidazole, DMAP) of **16** followed by *N*-deprotection (CAN, MeCN/H_2O = 3:1) afforded 2-pyrrolidinone **18**. Treatment of **18** with di(*tert*-butyl) dicarbonate (NEt_3, CH_2Cl_2) then furnished known **19** {$[\alpha]^{20}_D$ +34.3 (*c* 1.0, $CHCl_3$) [lit.[17e] $[\alpha]^{23}_D$ +37.9 (*c* 1.20, $CHCl_3$)] in 97% yield. The dextrorotary property of thus synthesized **19** clearly indicated its (4*S*,5*S*) absolute configuration[17e] and thus confirmed the above-mentioned stereochemical assignment of the reaction of lithiated **9** with alkyl halides.

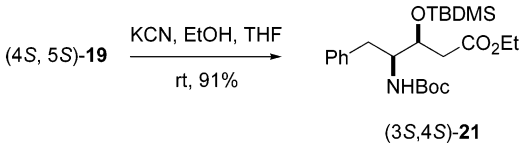
The diastereoselective installation of the nonyl group was achieved by a known one-pot procedure (*n*-$C_9H_{19}MgBr$; Et_3SiH, $BF_3{-}OEt_2$, −78 °C),[17e,k] which provided **20** {$[\alpha]^{20}_D$ −48.6 (*c* 1.1, $CHCl_3$) [lit.[17e] $[\alpha]^{25}_D$ −46.4 (*c* 1.50, $CHCl_3$)]} as the sole diastereomer. Heating a suspension of **20** and an excess of lithium aluminum hydride in THF for 28 h[18] gave (+)-preussin **4** {$[\alpha]^{20}_D$ +21.9 (*c* 1.3, $CHCl_3$) [natural **4**,[4] $[\alpha]^{25}_D$ +22.0 (*c* 1.0, $CHCl_3$)]} in 91% yield. The ^1H and ^{13}C NMR spectral data of synthetic material were identical with those of natural **4**.[4]

Scheme 6



Since **19** is a ready precursor to protected (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA, **6**), the synthesis of the latter was considered. Thus, stirring a mixture of **19** and a catalytic amount of potassium cyanide[19] in a mixed EtOH/THF (1:1, v/v, rt) solvent system led smoothly to the formation of *N*-Boc-(3*S*,4*S*)-4-amino-3-hydroxypentanoic acid ethyl ester **21** {colorless oil, $[\alpha]^{20}_D$ −23.4 (*c* 0.7, MeOH)}, a fully protected form of AHPPA, in 91% yield. AHPPA[20] is a key component found in naturally occurring aphatinins,[21] a protease inhibitor.

Scheme 7



In summary, the anion derived from **9** undergoes highly C-5 regioselective and diastereoselective reaction with alkyl halides to afford 5-alkyltetramic acid derivatives in good yields. The successful trapping of the carbanionic intermediate by TMSCl served to demonstrate its structure. The application of the present method to the asymmetric synthesis of (+)-preussin and a fully protected form of (3*S*,4*S*)-AHPPA both confirms the stereochemistry of the reaction and illustrates the versatility of the method.

Acknowledgment. The authors are grateful to the NNSF of China (29832020; 20072031; 20272048; 203900505) for financial support.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035617A

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