A Flexible Approach for the Asymmetric Synthesis of N-Protected (*R*)-5-Alkyl Tetramates and (*R*)-5-Alkyl Tetramic Acid Derivatives

Pei-Qiang Huang,* Jun Deng

Department of Chemistry and The Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, Fujian 361005, P. R. China
Fax +86(592)2186400; E-mail: pqhuang@xmu.edu.cn

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Dedicated to Professor Dr. Khi-Rui TSAI on the occasion of his 90th birthday.

Abstract: A flexible two-step asymmetric approach to N-protected (*R*)-5-alkyl tetramates and (*R*)-5-alkyl tetramic acid derivatives is described. The method is based on the diastereoselective alkylation of (*R*)-phenylglycinol derived tetramates **7** and **8**, which are the first synthetic equivalents to chiral nonracemic tetramate 5-carbanionic synthons **A**.

Key words: asymmetric synthesis, alkylations, chiral auxiliaries, tetramates, tetramic acids

5-Alkyl tetramic acids **1** are sub-structures found in a number of bioactive natural products.[1] Some of them exist as 'methyl ester', namely, methyl 5-alkyl tetramates **2**.[1] For example, methyl 5-methyl tetramate **2a** is found both in mirabimide E (**3**, Figure 1),[2] a solid tumor selective cytotoxin isolated from the terrestrial blue green alga *Scytonema mirabile* UH strain BY-8-1, and in dysideapyrrolidone,[3] a compound isolated from the tropical marine sponge *Dysidea herbacea* (*Dictyoceratida*) of specimen *D. herbacea* from Palau; dolapyrrolidone (Dpy) **2b** is a component of antineoplastic dolastatin 15, isolated in minus amount (1600 kg of mollusk yielded 6.2 mg!) from the Indian Ocean sea hare *Dolabella auricularia*.[4] In addition, the multiple functionalities and reactivities possessed by **1** and **2** render them versatile building blocks for the synthesis of other classes of bioactive natural products, which include indocarbazole natural product K252a,[5] β-hydroxy-γ-amino acids such as statine and AHPPA,[6,7] and pyrrolidine alkaloids.[7,8]

Since methods have been developed for the introduction of both C-3 and N-1 substituents starting from 5-alkyl tetramates,[9] the key to the asymmetric synthesis of C-3, C-5 and N-1 substituted tetramic acid-related natural products depends on the synthesis of 5-alkyl tetramic acids **1** or 5-alkyl tetramates **2**. Up to date, α-amino acid-based methods [6,10] remain the main entrance to optically active 5-alkyl tetramic acid-related natural products.[11] However, partial racemization has been observed in such approach.[12] Moreover, it was reported that the conversion of 5-alkyl tetramic acids to methyl 5-alkyl tetramates, by treatment of 5-alkyl tetramic acids either with dimethylsulfate or diazomethane[2,13] or with methanol under

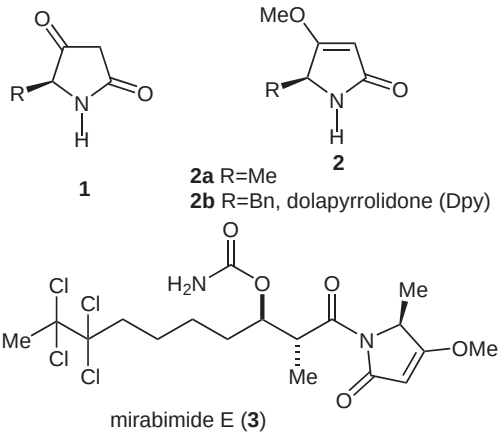

Figure 1

Mitsunobu conditions,[14] could not proceed without racemization. Thus the development of direct entrances[15] to chiral nonracemic tetramates is highly desirable. Very recently, we have reported a flexible approach to (*S*)-5-alkyl tetramic acid derivatives,[7] we now wish to report the first direct asymmetric approach to N-protected alkyl (*R*)-5-alkyl tetramates, which is based on the use of (*R*)-phenylglycinol as a N-chiral auxiliary.

The use of (*R*)-phenylglycinol as a chiral auxiliary for the asymmetric synthesis of N-containing compounds has enjoyed great success, which is due largely to Husson and co-workers' efforts in developing CN(*R*,*S*) methodology.[16] The alkylation of the (*R*)-phenylglycinol derived vinylogous enolates **4** (Figure 2) has also been studied, which was shown to occur exclusively at the C-3 position.[17] Only the corresponding silyl dienolethers (2-silyloxypyrrole) **5**[18] and **6**,[19] or the vinylogous enolates of N-protected 4-alkyl-3-pyrrolin-2-one[20] can react regioselectively with electrophiles at the C-5 position. However, such methods can neither be used for the synthesis of tetramates, nor allow the introduction of simple alkyl group at the C-5 position. Gratefully, it was reported that the reaction of achiral tetramate lithium dienolates with alkylating agents occurred regioselectively at the C-5 position.[21] On the basis of these considerations, we reasoned that the (*R*)-phenylglycinol derived chiral tetramates **7**/**8** would serve as suitable chiral building blocks for the asymmetric synthesis of 5-alkyl tetramates **9**/**10** (Scheme 1).

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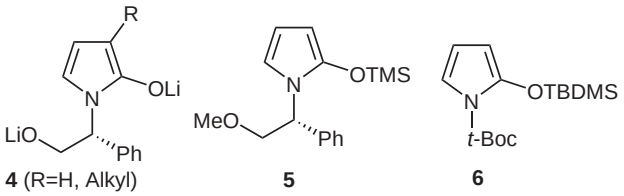
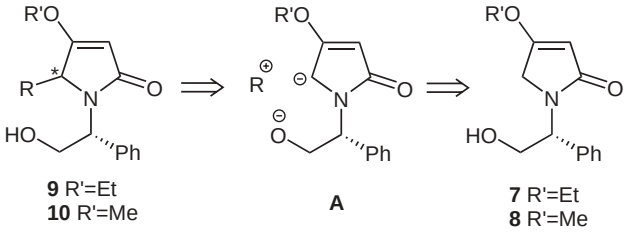
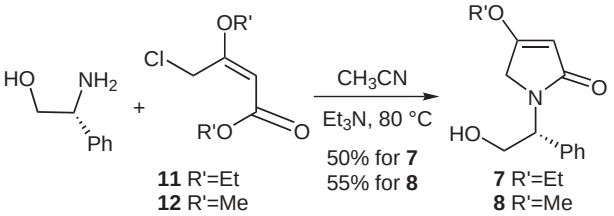


Figure 2



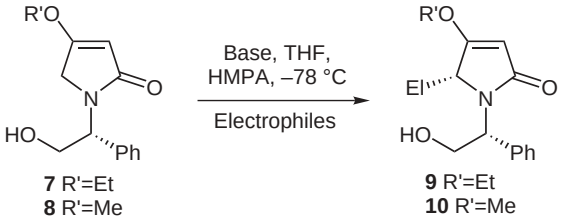
Scheme 1

Several methods are available for the preparation of 5-unsubstituted tetramates.[22] The required chiral tetramate **7** was synthesized by heating a acetonitrile solution of known ethyl (*E*)-4-chloro-3-ethoxy-2-butenoate (**11**)[22b,c] and (*R*)-phenylglycinol in the presence of triethylamine, which gave the desired N-protected ethyl tetramate **7** (white crystals, mp 114–115 °C) in 50% yield. Attempts to improve the yield of the condensation reaction by using pyridine or K_2CO_3 instead of triethylamine or by using *O*-TBDMS protected phenylglycinol were not rewarding. Although the yield of **7** is only 50%, its ready availability in just one step makes this approach attractive. Similar treatment of (*R*)-phenylglycinol with **12** afforded the corresponding N-protected methyl tetramate **8** in 55% yield (Scheme 2).



Scheme 2

With quantities of synthon equivalents **7** and **8** available, the generation of the dianions **A** (R′ = Et, Me) and subsequent reaction with electrophiles (Scheme 3) were investigated. As a first investigation, compound **7** was deprotonated with 2.4 molar equivalents of *tert*-butyllithium in THF at –78 °C, the anion generated in situ was quenched with deuteriomethanol (MeOD, –78 °C, 20 min), which yielded the C-5 deuterio product **9a** and the recovered starting material **7** in a ratio of 84:16 (yield 85%, Table 1, entry 1) as indicated by ^{1}H NMR spectral analysis. The deuterio product **9a** and the starting material **7** can be easily distinguished by ^{1}H NMR: the C-5 proton signal for **9a** appears at δ = 3.65 ppm as a broad singlet, whereas those of **7** exhibit as an AB system, which appear at δ = 3.64 and 3.82 ppm (J = 17.6 Hz). Except for the H-5 signal, both the ^{1}H NMR and ^{13}C NMR spectra of **9a** and **7** are identical, which indicates that the reaction occurred regioselectively at the C-5 position.



Scheme 3

Encouraged by this result, the alkylation of the dianionic intermediate **A** (R′ = Et) was pursued. Thus successive treatment of **7** with 2.4 equivalents of *t*-BuLi and methyl iodide in a mixed solvent system (THF–HMPA 20:1) at –78 °C for 6 hours afforded readily separable **9b** and its diastereomer in a ratio of 90:10 (combined yield 63%). Besides, 7% of recovered starting material **7** and 15% of dimethylated products were also isolated as an un-separable mixture (Table 1, entry 2).[23] Because we were unable to obtain the dimethylated side products in pure form, their structure and ratio could not be determined. Methylation of **8** proceeded similarly, which afforded **10b** in 90:10 diastereoselectivity (combined yield 72%, Table 1, entry 3). Alkylation of the dianion **A** (R′ = Et) in situ generated from **7** with other electrophiles gave the corresponding C-5 alkylated products in similar diastereoselectivities and chemical yields (Table 1, entries 4–6). When benzyl bromide was used as an alkylating agent, a slightly lower diastereoselectivity was obtained (Table 1, entries 7, 8). It is important to note that, only in the case showed in entry 7 (Table 1), did a small amount (8.6%) of the C-3 alkylated product was obtained.

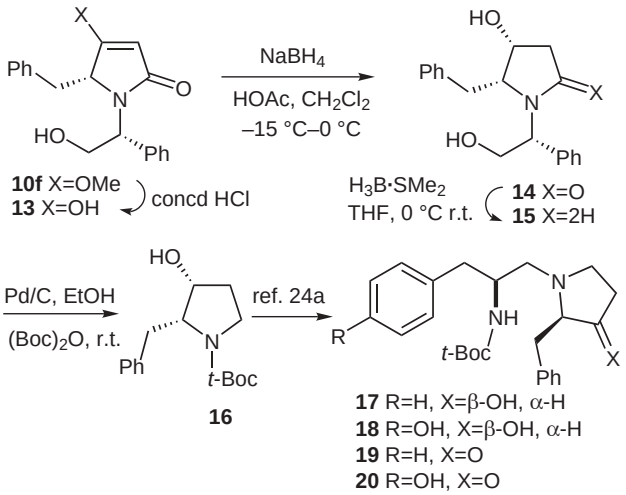
The recovering of a small amount of starting **7** or **8** in all cases might implicate that the deprotonation of the C-5 proton was uncompleted. It is important to note that the use of *tert*-butyllithium as the base is crucial for the reaction. Other bases such as *sec*-butyllithium or lithium hexamethyldisilazide gave poorer yields (Table 1, entries 9, 10).

To determine the stereochemistry of the alkylated products **9**/**10**, the transformation of methyl 5-benzyl tetramate **10f** into known 2-benzylpyrrolidin-3-ol (**16**)[24] was undertaken (Scheme 4). Thus treatment of **10f** with concentrated HCl solution for 12 hours gave tetramic acid **13**, which without further purification, was treated with sodium borohydride in a mixed solvent system (HOAc:CH_2Cl_2 = 1:10) at low temperature (–15 to 0 °C),[24a] to provide *cis*-**14** as the only observable product. The yield over two steps was 67%. The *cis* stereochemistry of compound **14** was assigned on the basis of observed vicinal coupling constants ($J_{4,5}$ = 5.2 Hz).[25]

Table 1 Results for the Reaction between Lithiated Compounds **7**/**8** and Electrophiles

Entry	Base/starting tetramates	Electrophiles	Products	Stereomeric ratio[a]	Yield (%)
1	*t*-BuLi/**7**	MeOD	**9a**:**7** (86:14)[b]	–[c]	(85)[e]
2	*t*-BuLi/**7**	MeI	**9b**	90:10[d]	63 (68)[e]
3	*t*-BuLi/**8**	MeI	**10b**	90:10[d]	72 (77)[e]
4	*t*-BuLi/**7**	EtI	**9c**	87:13[d]	68 (77)[e]
5	*t*-BuLi/**7**	*n*-BuI	**9d**	93:7[d]	61 (67)[e]
6	*t*-BuLi/**7**	*n*-$C_6H_{13}I$	**9e**	92:8[d]	63 (76)[e]
7	*t*-BuLi/**7**	BnBr	**9f**	84:16[d]	71 (83)[e]
8	*t*-BuLi/**8**	BnBr	**10f**	85:15[d]	58 (73)[e]
9	*s*-BuLi/**7**	*n*-$C_6H_{11}I$	**9e**	93:7[d]	49 (74)[e]
10	LHMDS/**7**	*n*-$C_6H_{13}I$	**9e**	87:13[d]	18 (49)[e]

[a] The stereochemistry of the major diastereomer was showed in **9**/**10** (Scheme 3), which was determined by chemical correlation (vide infra).
[b] Ratio determined by ^{1}H NMR.
[c] Ratio can not be determined by ^{1}H NMR.
[d] Ratio determined by chromatographical separation.
[e] Yields based on the recovered starting material.



Scheme 4

The reduction of amide **14** with borane dimethylsulfide complex ($H_3B{\cdot}SMe_2$) gave pyrrolidine **15**. Without further purification, **15** was subjected to hydrogenolysis conditions (H_2, l atm, 10% Pd/C, EtOH) in the presence of di(*tert*-butyl) dicarbonate to afford, in one-pot, the *N*-debenzylation–butoxycarbonylation product **16** {mp 78–79 °C; lit.[24a] mp 71 °C; $[\alpha]_D^{20}$ +5.8 (*c* 1.0, $CHCl_3$); lit.[24a] $[\alpha]_D^{23}$ +6.00 (*c* 1.0, $CHCl_3$) for 2*R*,3*R*-enantiomer; $[\alpha]_D^{23}$ –6.00 (*c* 1.0, $CHCl_3$) for 2*S*,3*S*-enantiomer}. The overall yield from **14** to **16** was 40%. The dextrorotary property of thus synthesized **16** clearly indicates its 2*R*,3*R* absolute configuration. Moreover, the present work provides a new approach to compounds **17**–**20**, which are novel potential HIV protease inhibitors.[24a]

All the products **9**/**10** show the same ^{1}H NMR and ^{13}C NMR spectral characteristics. This allows us to assume that they share the same stereochemistry as depicted in structure **9**/**10** (Scheme 3). With the stereochemistry ascertained, it is possible to have an insight into the stereochemical course of the alkylation reaction. It is reasonable to assume that the reaction passed through the chelating intermediate **B** or vinylogous enolate **C** (Figure 3). The reaction of **B** with electrophiles then proceeded with inversion of configuration[26] at the C-5 position, which would establish the *R*-configuration at the C-5. On the other hand, if the intermediate **C** was involved, then the electrophiles would approach from the *re*-face of the vinylogous enolate to avoid the unfavorable interaction with the phenyl group, which would establish *R*-configuration as well.

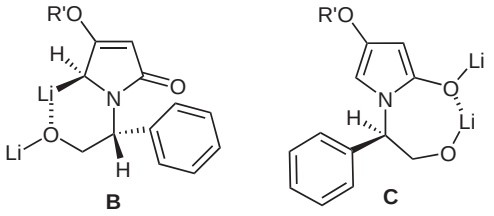


Figure 3

In summary, starting from (*R*)-phenylglycinol, we have developed a simple, versatile and direct two-step asymmetric approach to N-protected (*R*)-5-alkyl-tetramates and (*R*)-5-alkyl-tetramic acid derivatives. Among thus synthesized (*R*)-5-alkyl tetramate derivatives, methyl (*R*)-5-methyl-tetramate and methyl (*R*)-5-benzyl-tetramate are antipodes of the tetramate sub-units found respectively in mirabimide E (**3**), dysideapyrrolidone, and antineoplastic dolastatin 15. The transformation of the major diastereomer **10f** into known *N*-Boc-(2*R*,3*R*)-2-benzylpyrrolidin-3-ol (**16**) both confirms the stereochemistry of the reaction and provides an approach to some novel potential HIV protease inhibitors. Work is in progress for the asymmetric synthesis of naturally occurring tetramates.

Acknowledgment

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(23) **Representative Procedure for the Alkylation of (*R*)-7/8**: To a solution of (*R*)-**7** (104 mg, 0.42 mmol) in THF (8.4 mL, containing 0.37 mL of HMPA as a co-solvent) was added dropwise *t*-BuLi (0.67 mL, 1.5 M in pentane) at –78 ºC. After being stirred for 1 h, MeI (0.08 mL, 1.26 mmol) was added and the stirring continued for an additional 6 h at the same temperature. The reaction was quenched by sat. NH_4Cl. The resulting mixture was extracted with Et_2O, and the organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel to give **9b** (62 mg, colorless oil), its diastereomer (7 mg, pale yellow oil) (combined yield, 63%) and recovered **7** (7 mg, yield based on the recovered starting material, 68%). Compound **9b**: $[\alpha]_D^{20}$ +19.4 (*c* 1.1, $CHCl_3$). IR (KBr): 3374, 2981, 2934, 1657, 1625, 1340, 1221, 1029 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, Ar*H*), 5.18 (dd, *J* = 6.4, 7.7 Hz, 1 H, D_2O exchangeable, O*H*), 5.01 (s, 1 H, O=CC*H*=), 4.51 (dd, *J* = 3.1, 7.7 Hz, 1 H, PhC*H*N), 4.27 (ddd, *J* = 7.7, 7.7, 12.3 Hz, 1 H, HOCH_2), 4.00 (m, 3 H, CH_3CH_2O and HOCH_2), 3.73 (q, *J* = 6.8 Hz, 1 H, CH_3CHN), 1.37 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 1.28 (d, *J* = 6.8 Hz, 3 H, CH_3CHN) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.42, 173.18, 138.34, 128.80 (2 C), 127.77, 127.05 (2 C), 93.35, 67.10, 64.91, 61.90, 57.17, 15.83, 14.06 ppm. MS (ESI): *m/z* (%) = 262 (13) [M + H^+], 244 (5) [M + H^+ – H_2O], 142 (100). HRMS calcd for [$C_{15}H_{19}NO_3$ + H]$^+$: 262.1438. Found: 262.1440. Minor diastereomer of **9b**: $[\alpha]_D^{20}$ +17.1 (*c* 1.1, $CHCl_3$). IR (KBr): 3367, 2981, 2932, 1659, 1625, 1340, 1222, 1029 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, Ar*H*), 5.02 (s, 1 H, =C*H*C=O), 4.82 (dd, *J* = 3.8, 7.5 Hz, PhC*H*N), 4.21 (m, 1 H, HOCH_2N), 4.09 (m, 2 H, HOCH_2 and O*H*), 3.98 (m, 2 H, CH_3CH_2O), 3.88 (q, *J* = 6.8 Hz, 1 H, CH_3CHN), 1.37 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 1.14 (d, *J* = 6.8 Hz, 3 H, CH_3CHN). MS (ESI): *m/z* (%) = 262 (100) [M + H^+]. HRMS calcd for [$C_{15}H_{19}NO_3$ + H]$^+$: 262.1438. Found: 262.1432.
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