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Mild Construction of 3-Methyl Tetramic Acids Enabling a Formal Synthesis of Palau'imide

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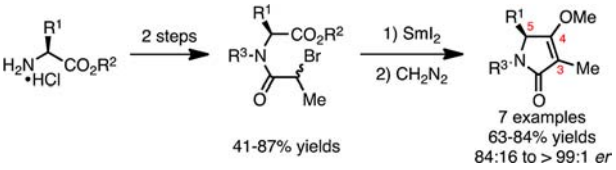
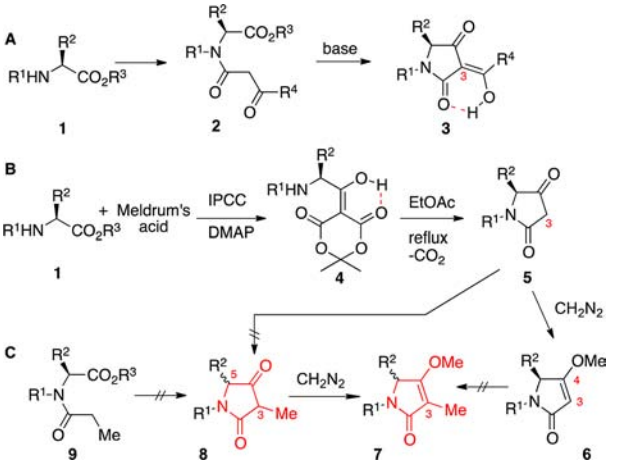
ABSTRACT



A general method to construct 3-methyl-4-*O*-methylated tetramic acids displaying a C-5 stereocenter is presented. The synthetic sequence employs a SmI_2-mediated cyclization, whereby the chirality of the emerging tetramic acid core is retained from the starting chiral amino acid. Application to palau'imide is discussed.

Chiral tetramic acids display an assortment of desirable biological activities.[1] In most cases, their underlying heterocyclic structure incorporates either an acyl or hydrido substituent at their C-3 position. Among their 4-*O*-alkyl ether variations, only the *O*-methylated form is seen in nature.[2] The medicinal value of these assorted compounds prompted the emergence of several synthetic methods, the first appearing in 1972.[3] Since then, two procedures among these have risen to become generally accepted and have been used in nearly all syntheses (Scheme 1A and B).[4] For unracemized acyl derivatives of **3**, the Lacey Dieckmann procedure is most often used, whereby the amino acid derivative **1** is converted into the 1,3-dione **2** and then subjected to cyclization.[5] An answer for the preparation of the hydrido counterpart **5** proved to be more challenging. Jouin eventually reported using the amino acid **1** in conjunction with Meldrum's acid to afford the acyl derivative **4**, which undergoes cyclization and decarboxylation resulting

Scheme 1. Methods for Tetramic Acid Construction Are Unsuitable for Fabrication of C-3 Methyl Tetramic Acid Derivatives



(1) For reviews on isolation and synthesis of tetramic acids, see: (a) Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981. (b) Schobert, R.; Schlenk, A. *Bioorg. Med. Chem.* **2008**, *16*, 4203.

(2) Paik, S.; Carmeli, S.; Cullingham, J.; Moore, R. E.; Patterson, G. M. L.; Tius, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 8116.

(3) Mulholland, T. P. C.; Foster, R.; Haydock, D. B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2121.

(4) For examples for total synthesis of natural products containing tetramic acid with Lacey Dieckman and Jouin's protocols, see: (a) Boeckman, R. K., Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036. (b) Turos, E.; Audia, J. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8231. (c) Gu, Z.; Zakarian, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9702. (d) Hart, A. C.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 1094. (e) Pronin, S. V.; Martinez, A.; Kuznedelov, K.; Severinov, K.; Shuman, H. A.; Kozmin, S. A. *J. Am. Chem. Soc.* **2011**, *133*, 12172.

(5) (a) Lacey, R. N. *J. Chem. Soc.* **1954**, 850. (b) Fitch, D. M.; Evans, K. A.; Chai, D.; Duffy, K. J. *Org. Lett.* **2005**, *7*, 5521.

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in the tetramic acid **5**.[6] This intermediate undergoes further *O*-methylation with diazomethane to produce compound **6** without any observed racemization, a significant problem due to the acidity of the C-5 hydrogen in these systems.[7]

However, the β-dicarbonyl strategies, which were used for ring formation in **A** and **B** of Scheme 1, are not adaptable to the construction of C-3 methyl derivatives, such as **7** and **8**. Moreover, most imagined reagent combinations employed with compounds **6** and **9** would be expected to either fail or corrupt the C-5 stereocenter.[8]

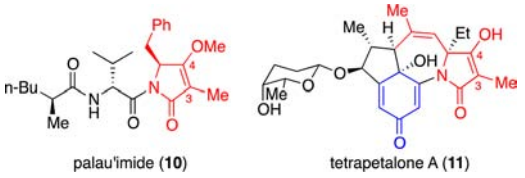


Figure 1. Natural compounds containing C-3 methyl tetramic acids.

In 2002, the first natural example of a C-3 methyl tetramic acid derivative, palau'imide (**10**), was isolated from the apratoxin producing marine cyanobacterium *Lyngbya* sp. in Palau and shown to exhibit cytotoxicity *in vitro* against KB and LoVo cells with IC_{50} values of 1.4 and 0.36 μM respectively (Figure 1).[9] One year later, the C-3 methyl tetramic acid derivative tetrapetalone A (**11**) and three other derivatives were isolated from soil bacteria *Streptomyces* sp. USF-4727 in Japan.[10] Compound **11** was found to inhibit soybean lipoxygenase (SBL), displaying an IC_{50} = 190 μM, which compared favorably to the most potent SBL inhibitors known, kojic acid (IC_{50} = 110 μM) and nordihydroguaiaretic acid (NDGA, IC_{50} = 290 μM). These recent discoveries catapulted the quest for a general method enabling the mild preparation of C-3 methyl tetramic acid derivatives back to the forefront of synthetic research.

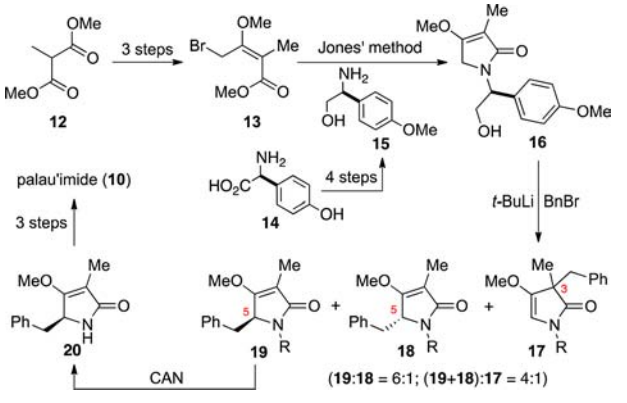
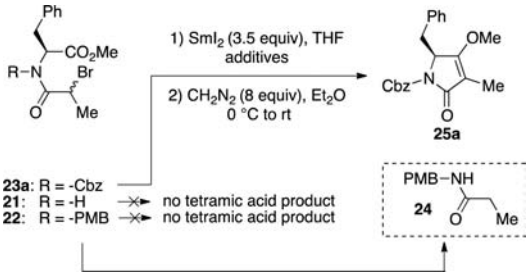


Figure 2. Huang's prior synthesis of palau'imide (**10**).[11]

Huang and co-workers answered this call in 2010, reporting the first synthesis of palau'imide (**10**) (Figure 2).[11] The strategy was predicated upon an early bromination and amine cyclization protocol used by Jones to access C-3 hydrido derivatives.[12] They prepared the bromide **13** from 1,3-dicarbonyl compound **12** and showed it to undergo reaction with optically pure β-amino alcohol **15**, previously synthesized from (*S*)-*p*-hydroxyphenylglycine **14**, so as to afford C-3 methyl tetramic acid **16**. This optically pure material **16** underwent C-benzylation favoring the desired C-5 benzylation regioisomer over the C-3 isomer (**19:18** = 6:1; ((**19** + **18**):**17** = 4:1)). After separation of these compounds, cerium ammonium nitrate (CAN) mediated oxidative cleavage of the *p*-methoxy-benzylated nitrogen substituent from adduct **19** afforded the C-3 methyl tetramic acid **20** that was carried for three more steps to produce palau'imide (**10**).

Instead of the traceless diastereocontrol protocol described above, we aimed to develop a more general protocol, whereby the chirality within the tetramic acid core might be retained from a starting chiral amino acid used during its construction. To this end, we decided to explore a samarium diiodide mediated cyclization, long advocated by Molander.[13] Herein, we report our findings.

Table 1. Survey of Protecting Groups and Additives for Yield Optimization in SmI_2-Mediated Cyclizations



entry	R	*t* (°C)	equiv of additive	additive(s)	yield (%)[a]
1	H	23	0–10	various	0
2	PMB	23	0–10	various	0[b]
3	Cbz	23	0	none	14
4	Cbz	23	0.1	$Fe(acac)_3$	18
5	Cbz	23	10	HMPA	31
6	Cbz	−10	10	HMPA	20
7	Cbz	−40	10	HMPA	<5
8	Cbz	0	10	DMPU	45
9	Cbz	0	5	HMPA	62
10	**Cbz**	**0**	**10**	**HMPA**	**65**

[a] Isolated two-step yield. [b] Compound **24** was isolated in 70% yield.

(6) (a) For a review of Meldrum's acid in the synthesis of tetramic acids, see: Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789. (b) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177.

(7) (a) Hosseini, M.; Kringelum, H.; Murray, A.; Tønder, J. E. *Org. Lett.* **2006**, *8*, 2103. (a) Jin, Y.; Liu, Y.; Wang, Z.; Kwong, S.; Xu, Z.; Ye, T. *Org. Lett.* **2010**, *12*, 1100.

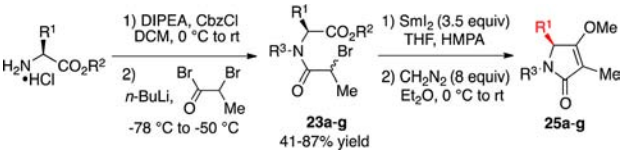
(8) Poncet, J.; Jouin, P.; Castro, B.; Nicolas, L.; Boutar, M.; Gaudemer, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 611.

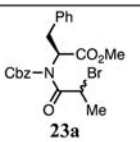
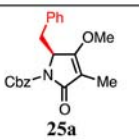
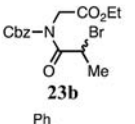
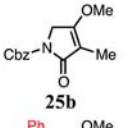
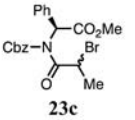
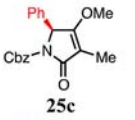
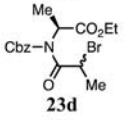
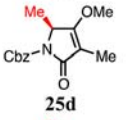
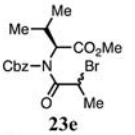
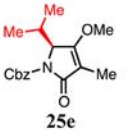
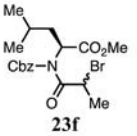
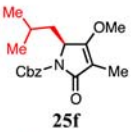
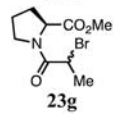
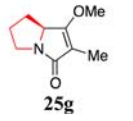
(9) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *Tetrahedron* **2002**, *58*, 7959.

We began by preparing several L-phenylalanine derivatives, **21**–**22** and **23a**, from 2-bromopropionyl bromide using standard procedures and then examined the ensuing cyclizations mediated by samarium iodide (SmI_2) (Table 1). Reactions of the unprotected amide **21** failed to give any of the desired adduct under various conditions and returned the corresponding *des*-bromo material (entry 1). Much to our surprise, a variety of conditions employing corresponding NH-protected *para*-methoxybenzyl (PMB) derivative **22** also failed to afford the desired tetramic acid and resulted instead in the aniline **24** from an unanticipated cleavage (Table 1, inset). Preliminary studies with the PMB protected glycine derivative (not shown) also failed to produce the corresponding tetramic acid and led to the amide **24** upon SmI_2 treatment. We were therefore gratified to find the NH protected benzyloxycarbonyl (Cbz) bromide **23a** gave the desired tetramic acid **25a**, albeit in a paltry 14% yield (entry 3) upon exposure to a freshly prepared SmI_2 solution (3.5 equiv, 0.1 M in THF) followed by aqueous workup and exposure to diazomethane (8.0 equiv, 0.4 M in Et_2O). Use of $Fe(acac)_3$[13b] (0.1 equiv) led to a slight improvement (18% yield, entry 4), whereas addition of HMPA[13a] (10 equiv) increased the yield even further to 31% (Table 2, entry 5). Lowering the temperature of the reaction to either −10 or −40 °C thwarted product formation (entries 6–7). Switching the additive to DMPU and raising the temperature to 0 °C afforded a slight gain (entry 8).[13c,d] Upon reinvestigation of HMPA, we found 0 °C with 5–10 equiv of the additive at 0 °C to provide the optimum yield (entries 9–10).

We therefore turned our attention toward retention of the enantiomeric integrity within compound **25a** and other derivatives emerging from this method (Table 2). The starting α-bromides **23a**–**f** for these experiments were prepared from their respective *nonracemic* amino esters in yields ranging from 41 to 60% for the two-step transformation, one chromatography sequence. On the other hand, the proline derivative **23g** was prepared from L-proline methyl ester hydrochloride and 2-bromopropionyl bromide in an 87% yield. Each of these epimeric bromides was then individually subjected to samarium iodide. Treatment of the respective optically active cyclization adducts (**25a**–**d**, **25f**) with KO*t*-Bu (potassium *tert*-butoxide, 2.0 equiv) provided the corresponding racemic product in under a minute for subsequent comparative HPLC studies.[7a] This process underscores the challenge of devising a base mediated cyclization protocol that retains the enantiomeric integrity of the starting amino acid.[14] Standards for **25e** and **25g**, which proved difficult to racemize in this manner, were prepared from the corresponding *racemic* amino acid.

Table 2. Scope of SmI_2-Mediated Cyclization to Construct 3-Methyl-4-*O*-methylated Tetramic Acids **25**



entry	substrate **23a-g**	product **25a-g**	yield (%)[a]	*er*[b]
1	 **23a**	 **25a**	65	92:08
2	 **23b**	 **25b**	84	-
3	 **23c**	 **25c**	75	84:16
4	 **23d**	 **25d**	80	95:05
5	 **23e**	 **25e**	77	95:05
6	 **23f**	 **25f**	78	93:07
7	 **23g**	 **25g**	63	>99:01

[a] Isolated two-step yield of **25**. [b] Enantiomeric ratios (*er*) were determined by HPLC.

The 92:8 *er* measured by HPLC for adduct **25a** indicated a slight loss of integrity during the course of the cyclization process (Table 2, entry 1).[13a,b] Concerned about the effect of HMPA on the basicity of the reaction, we halved its equivalents. This change led to a sluggish reaction displaying a comparable ratio. We theorized that perhaps SmI_2OMe formed during the course of the reaction might be responsible for the loss of integrity and, therefore, added ethyl acetate in the hopes of consuming it. While improving the *er*, this modification lowered the yield. We therefore

(10) (a) Komodo, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Hirota, A. *Tetrahedron Lett*. **2003**, *44*, 1659. (b) Komodo, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Tetrahedron Lett*. **2003**, *44*, 7417. (c) Komoda, T.; Kishi, M.; Abe, N.; Sugiyama, Y.; Hirota, A. *Biosci. Biotechnol. Biochem*. **2004**, *68*, 903.

(11) Lan, H.-Q.; Ruan, Y.-P.; Huang, P.-Q. *Chem. Commun*. **2010**, *46*, 5319.

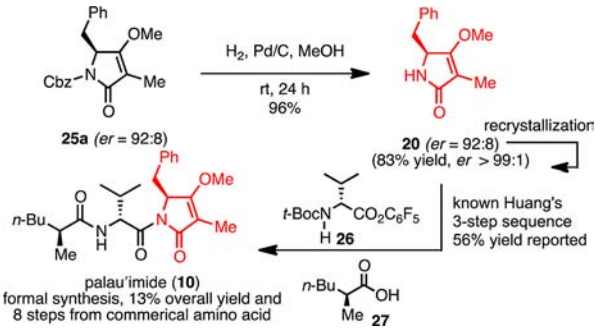
(12) Jones, R. C. F.; Bates, A. D. *Tetrahedron Lett*. **1986**, *27*, 5285.

(13) (a) Molander, G. A.; Mckie, J. A. *J. Org. Chem*. **1992**, *57*, 3132. (b) Molander, G. A.; Mckie, J. A. *J. Org. Chem*. **1993**, *58*, 7216. For reviews on SmI_2 catalyzed reactions, see: (c) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (d) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev*. **2004**, *104*, 3371.

(14) During the preparation of this manuscript we learned of a telluride-mediated Dieckmann cyclization of *N*-benzyl protected α-bromoacyl amides. However, the enantiomeric integrities of products were not determined: Dittmer, D. C.; Avilov, D. V.; Kandula, V. S.; Purzycki, M. T.; Martens, Z. J.; Hohn, E. B.; Bacler, M. W. *ARKIVOC* **2010**, *vi*, 61.

maintained our original conditions when examining subsequent examples. Our general 10 equiv, 0 °C protocol tolerates a variety of substituents at the C-5 position and in most instances affords a similar ratio to that of entry 1 (entries 2−7). The enantiomeric integrity of the cyclization adduct could be restored to nearly >99:1 by a single recrystallization after cleavage of the protective Cbz group. The lower initial *er* observed for the phenyl derivative **25c** likely reflects its propensity toward enolization (entry 3). Whereas the improved *er* for **25g** suggests a decreased enolization due to angle strain afforded by ring fusion (entry 7).

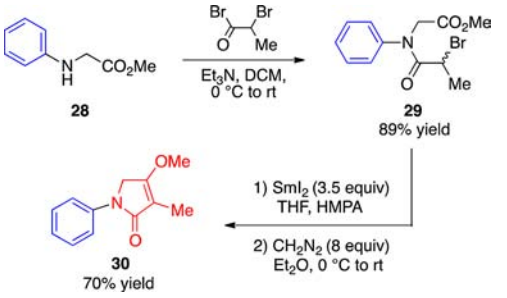
Scheme 2. Formal Synthesis of Palau'imide (**10**)



A demonstration of the utility of our new general method emerges from consideration of the formal synthesis of palau'imide (**10**) by interception of the Huang intermediate **20** (Scheme 2). The Cbz protecting group of **25a** (*er* = 92:8) was cleaved with H_2 over Pd/C conditions to afford the free tetramic acid in a 96% yield. Recrystallization afforded compound **20** (83% yield, >99:1 *er*). As the remainder of the synthesis is reported to proceed in 56% yield,[11] this method would be anticipated to afford palau'imide (**10**) in eight steps, six pots, and 13% overall yield.

Additional studies have shown that this SmI_2-mediated cyclization also proceeds with *N*-aryl glycine derivatives such as **29** to give the *N*-phenyl tetramic acid **30** in moderate yield (Scheme 3). Therefore, this method may offer a concise and efficient way to construct the tetrapetalone family. The method also provides a solution to the challenging task of preparing *N*-aryl tetramic acid intermediates expressing C-3 functionalization.

Scheme 3. SmI_2-Mediated Cyclization of *N*-Aryl Glycine Derivative **29**



In conclusion, we have disclosed a general method to construct C-3 functional tetramic acids that are optically active bearing a C-5 stereocenter. The synthetic sequence employs a nonbasic SmI_2-mediated cyclization and nearly maintains the enantiomeric integrity of the starting chiral amino acid. The cyclization tolerated the Cbz being protected as well as *N*-aryl amino acids derivatives, and it is operable on a multigram scale. Application in an operationally simplified synthesis of palau'imide (**10**) was discussed. A report of the application of this method toward tetrapetalone A (**11**) may be disclosed in the future.

Acknowledgment. T.R.R.P. is very grateful that the National Institute of General Medical Sciences has supported this work (GM064831) and other studies related to the synthesis of the tetrapetalones.

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

The authors declare no competing financial interest.