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Synthetic approaches to the southern part of cyclotheonamide C

David J. Aitken,* Sophie Faure and Stéphane Roche

Laboratoire SEESIB-CNRS (UMR 6504), Département de Chimie, Université Blaise Pascal—Clermont-Ferrand II, 24, Avenue des Landais, 63177 Aubière cedex, France

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Abstract—A synthetic equivalent of the southern segment of cyclotheonamide C, a cyclopentapeptide isolated from the sponge *Theonella*, has been synthesized via complementary Wadsworth–Emmons or palladium-catalysed methodologies followed by tandem oxidation/vinylogation in 41% overall yield (five steps) from readily available starting materials.

Over the last decade, a family of nine macrocyclic pentapeptides named cyclotheonamides (CtA–CtEn) has been isolated from *Theonella* and *Ircinia* sponges by the groups of Fusetani[1] and Murakami[2] (Fig. 1). These macrocyclic compounds contain unusual amino acid residues and act as powerful inhibitors of thrombin and other serine proteases (trypsin, plasmin, etc.).[1–4] Three residues (northern part) interact directly with the enzyme active site while the other two (southern part) play a structural role. The novel structure and potential therapeutic value of these compounds has stimulated considerable interest; however, only four cyclotheonamides have been prepared by total synthesis (CtA,[3,5] CtB,[6] CtE2,[7] CtE3[7]). Within the group, cyclotheonamide C (CtC) has the unique feature of a vinylogous α,β-dehydrotyrosine moiety v-ΔTyr.[1b] The present work describes the efficient synthesis of 'South-C' **1**, a key synthetic equivalent of the southern fragment C(12)–N(19) of CtC.

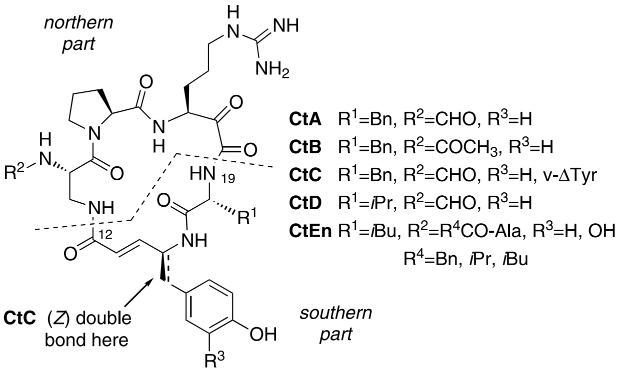

Figure 1. Members of the cyclotheonamide (Ct) family.

In particular, we have examined and compared two complementary routes leading to the α,β-didehydrotyrosine derivative **2**: via Wadsworth–Emmons reaction of a phosphorylglycine or via palladium-catalysed coupling of a dehydroalanine derivative (Scheme 1).

Previous work on dehydroamino acids[8] suggested that dipeptide **2** might be obtained by Wadsworth–Emmons reaction of the phosphonoglycine derivative **6** with the corresponding protected *p*-hydroxybenzaldehyde **7**. Compound **6** was obtained in 95% yield by coupling of *N*-Boc-D-Phe **5** and dimethoxyphosphorylglycine methyl ester **4**, the latter readily prepared by deprotection of its commercially available benzyl carbamate precursor **3** immediately before use (Scheme 2). The aldehyde partner **7** bearing a silyl ether protecting group was prepared simply from *p*-hydroxybenzaldehyde.[9] Wadsworth–Emmons reaction of **6** with **7** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at low temperature (−20°C) provided the dipeptide **2** in 74% yield in a *Z*/*E* ratio of 90/10. Use of other bases (NaH, *t*BuOK) gave lower yields (≤36%) and complete loss of *Z*/*E* selectivity (Table 1). The isomers of **2** were easily separated by flash chromatography on silica gel and the *Z* double bond configuration of the major isomer was assigned according to ^{1}H NMR analysis. Previous studies on dehydroamino acids have shown that the vinyl proton signal of the *E* isomer appears $\delta = 0.2$–0.7 ppm downfield from that of the *Z* isomer (Scheme 2).[10] This first convergent strategy provided pure (*Z*)-**2** in three steps from phosphorylglycine derivative **3** with a 62% overall yield.

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* Corresponding author. Tel.: +33-4-73-40-74-81; fax: +33-4-73-40-77-17; e-mail: aitken@chimie.univ-bpclermont.fr

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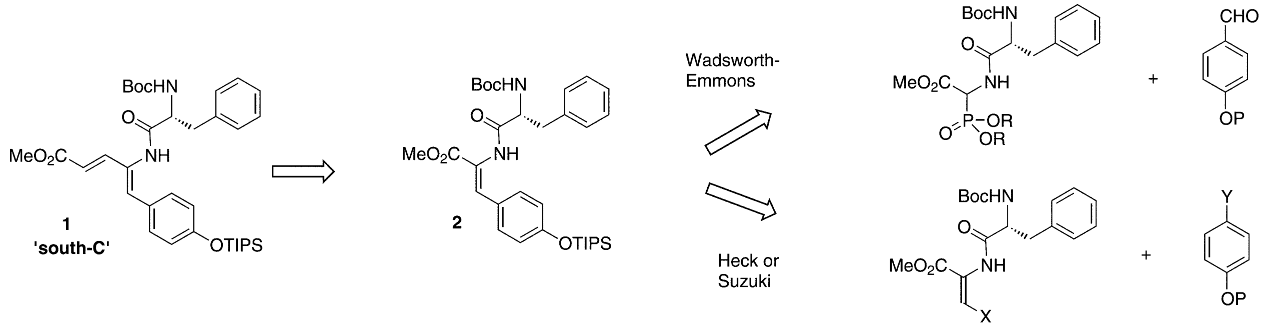
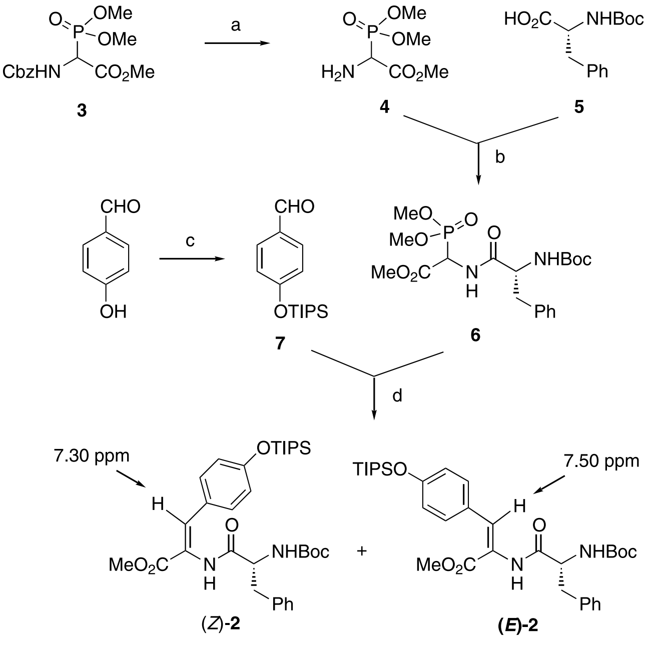


Scheme 1. Retrosynthetic analysis of **1**, a synthetic equivalent of the southern part of CtC.

The second strategy proceeds via the dehydroalanine (ΔAla) building block **10** and introduces the ΔTyr moiety by palladium-catalysed coupling (Scheme 1). The intermediate **10** was prepared in two steps and in 68% yield (Scheme 3). Coupling of *N*-Boc-D-Phe **5** and DL-Ser-OMe **8** provided the dipeptide **9** which was readily dehydrated using cuprous chloride and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI).[11] We first investigated the Heck coupling reaction.[12] Silyl ether protection of *p*-iodophenol gave compound **12** which was reacted with **10** in the presence of different catalytic systems (Scheme 3, Table 2). The coupling reaction provided the expected *Z* isomer exclusively, but in only 30–35% yield at best, due in part to incomplete conversion of the substrate. The most useful result was obtained with Herrmann's catalyst (palladium acetate and tris-*o*-tolylphosphine as ligand).[13] The absence of a phosphine ligand gave similar conversion but led annoyingly to cleavage of the silyl ether protecting group. The inefficiency of the Heck coupling is probably due to cumulative unfavorable electronic and steric effects, arising from the electron-rich iodoaryl component and the α,α-disubstituted alkene partner.

We therefore turned our attention towards the Suzuki coupling reaction.[14] In this case, the stereoelectronic effects prevalent in the alkene and aryl reacting partners should now promote the reaction.[15] The appropriate components—bromoalkene **11** and boronic acid derivative **13**—were synthesized from the dipeptide **10** and *p*-iodophenol **12**, respectively (Scheme 3).[16,17] Gratifyingly, Suzuki coupling provided the required compound **2** as a single *Z* isomer in 76% yield. The combination of two additives, ethanol and water, accelerates the reaction.[18] In the absence of water, the reaction time was longer and partial transesterification occurred. In the absence of both water and ethanol, the reaction was much less efficient (Table 2).

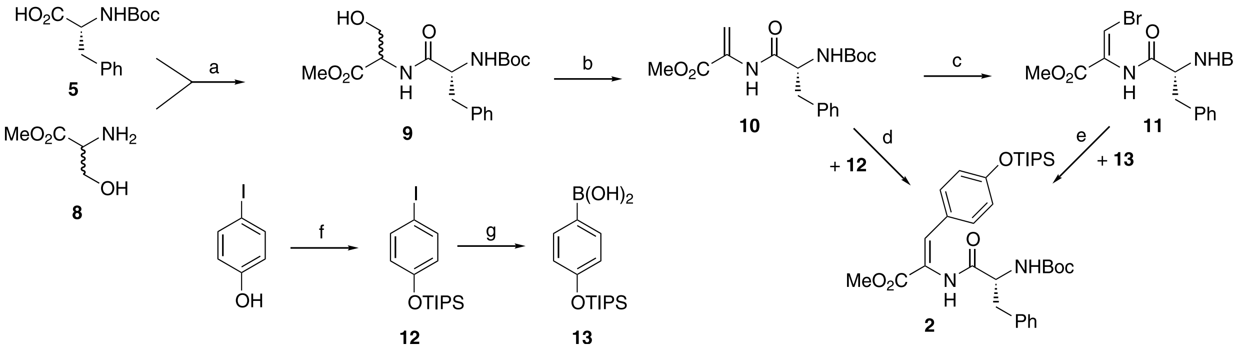
The last sequence of this synthesis of 'South-C' **1** is the vinylogation of compound **2** by conversion into the aldehyde **15** followed by a Wittig-type reaction (Scheme 4). Chemoselective reduction of intermediate **2** with $LiAlH_4$ gave primary alcohol **14** in high yield. Initial efforts to oxidize this alcohol to aldehyde **15** met with difficulty, due to product instability and considerable loss of material on attempted isolation and purification. We therefore carried out the subsequent vinylogation reaction on **14** after minimal work-up of the oxidation reaction. Several mild oxidants—Dess–Martin periodinane (DMP), manganese dioxide, O_2–TEMPO–CuCl[19]—were investigated prior to the Wadsworth–Emmons reaction with the anion of methyl diethylphosphonoacetate (Table 3). Only moderate yields (42–55%) of **1** were obtained. We therefore adapted the system for a 'one-pot' transformation, which required use of (carbomethoxymethylene)triphenylphosphorane as the nucleophile. A DMP-based protocol[20] was inefficient, but use of MnO_2[21] provided target compound **1** in 75% yield with exclusively the *E* configuration for the new double bond (Table 3).[22]



Scheme 2. *Reagents and conditions*: (a) H_2 (3 atm), 10% Pd/C, MeOH, quant.; (b) EDCI, HOBt, CH_2Cl_2, rt, 95%; (c) TIPS-Cl, imidazole, CH_2Cl_2, 95%; (d) see Table 1.

Table 1. Wadsworth–Emmons reaction of **6** with **7**

Entry	Conditions (d)	Yield of **2** (%)	*Z*/*E* ratio	Yield of (*Z*)-**2** (%)
1	*t*BuOK, CH_2Cl_2, −78°C	0	–	0
2	NaH, THF, −20°C	36	50/50	18
3	DBU, CH_2Cl_2, −20°C	74	90/10	67



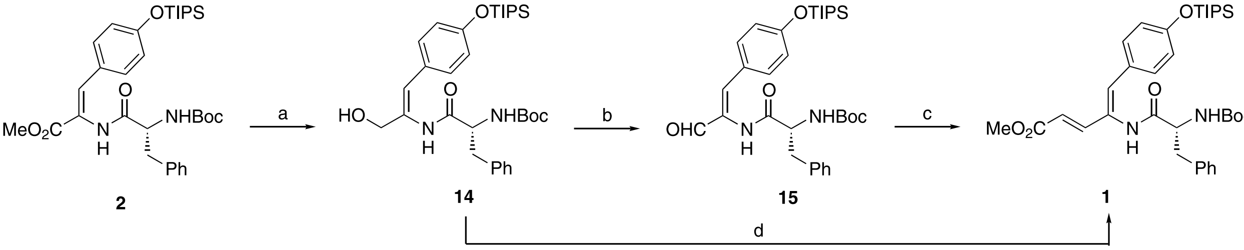
Scheme 3. *Reagents and conditions*: (a) Isobutyl chloroformate, Et_3N, DL-Ser-OMe, CH_2Cl_2, 87%; (b) EDCI, CuCl, CH_2Cl_2, 80%; (c) NBS, CH_2Cl_2 then Et_3N, 86%; (d) see Table 2; (e) see Table 2; (f) TIPSCl, imidazole, CH_2Cl_2, 94%; (g) *t*BuLi, B(O*i*Pr)$_3$, THF, −78°C then HCl (2 M), 58%.

Table 2. Palladium-catalysed Heck and Suzuki coupling reaction conditions

Entry	Alkene	Arene	Catalytic system	Solvent	Temperature	Time (h)	Yield of **2** (%)
1	**10**	**12**	3% Pd(OAc)$_2$, Bu_4NBr, $NaHCO_3$	DMF	100°C	24	34[a]
2	**10**	**12**	10% Pd(OAc)$_2$, 20% PPh_3, Et_3N	CH_3CN	Reflux	48	22
3	**10**	**12**	5% Pd(OAc)$_2$, 10% P(*o*-tolyl)$_3$, Et_3N	CH_3CN	Reflux	96	30
4	**11**	**13**	3% Pd(PPh$_3$)$_4$, K_2CO_3	Toluene	Reflux	48	16
5	**11**	**13**	3% Pd(PPh$_3$)$_4$, K_2CO_3, 20% EtOH	Toluene	Reflux	16	57[b]
6	**11**	**13**	3% Pd(PPh$_3$)$_4$, K_2CO_3, 20% EtOH, 10% H_2O	Toluene	Reflux	1	76

[a] Yield of the corresponding phenol, due to silyl ether cleavage.

[b] Partial transesterification occurred to provide the ethyl ester derivative with an additional 17% yield.



Scheme 4. *Reagents and conditions*: (a) $LiAlH_4$, THF, 0°C, 86%; (b) oxidation: see Table 3; (c) Wadsworth–Emmons: see Table 3; (d) 'one-pot' oxidation–vinylogation: see Table 3.

Table 3. Obtention of **1** by oxidation–vinylogation of compound **14**

Entry	Strategy	Conditions	Yield of **1** (%)
1	2 steps	(b) DMP (1.5 equiv.), py, CH_2Cl_2, 1 h; (c) $(EtO)_2POCH_2CO_2Me$/NaH (3 equiv.), THF, −0°C to rt, 1 h	42
2	2 steps	(b) MnO_2 (15 equiv.), CH_2Cl_2, Δ, 36 h; (c) $(EtO)_2POCH_2CO_2Me$/NaH (3 equiv.), THF, −0°C to rt, 1 h	49
3	2 steps	(b) TEMPO (0.1 equiv.), CuCl (0.1 equiv.), O_2, 12 h; (c) $(EtO)_2POCH_2CO_2Me$/NaH (3 equiv.), THF, −0°C to rt, 1 h	55
4	'One-pot'	(d) DMP (1.2 equiv.), $PhCO_2H$ (2 equiv.), $Ph_3P{=}CHCO_2Me$ (1.5 equiv.), CH_2Cl_2/DMSO, rt, 1 h	20
5	'One-pot'	(d) MnO_2 (20 equiv.), $Ph_3P{=}CHCO_2Me$ (1.5 equiv.), CH_2Cl_2, Δ, 24 h	75

In conclusion, two complementary synthetic approaches have led successfully to key compound **1**, a synthetic equivalent of the southern fragment C(12)–N(19) of cyclotheonamide C, bearing three mutually orthogonal protecting groups. The second route has the advantage of providing intermediate **2** via a fully stereoselective Suzuki coupling reaction. However, the phosphonoglycine-based strategy leading to **2** is more expedient (even allowing for chromatographic separation of stereoisomers). Beginning with this sequence, the target compound **1** was prepared in five steps from readily available materials with 41% overall yield.

Acknowledgements

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22. Compound **1**: white powder, mp 71–73°C, $[\alpha]_D^{25}=+68$ (c 1.6, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, $J=7.2$ Hz, 18H), 1.16 (hept, $J=7.2$ Hz, 3H), 1.34 (s, 9H), 3.00 (dd, $J=13.8$, 7.1 Hz, 1H), 3.13 (dd, $J=13.8$, 7.1 Hz, 1H), 3.64 (s, 3H), 4.51 (m, 1H), 5.08 (d, $J=8.4$ Hz, 1H), 5.59 (d, $J=15.4$ Hz, 1H), 6.53 (s, 1H), 6.67 (d, $J=8.6$ Hz, 2H), 7.13 (d, $J=8.6$ Hz, 2H), 7.15–7.26 (m, 6H), 7.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6 (3CH), 17.9 ($6CH_3$), 28.2 ($3CH_3$), 37.5 (CH_2), 51.4 (CH_3), 56.0 (CH), 80.6 (C), 116.8 (CH), 120.1 (2CH), 127.0 (CH), 127.1 (C), 128.6 (C), 128.8 (2CH), 129.4 (2CH), 131.2 (2CH), 135.0 (CH), 136.5 (C), 144.0 (CH), 155.9 (C), 157.0 (C), 167.3 (C), 170.4 (C). Elemental analysis calcd for $C_{35}H_{50}N_2O_6Si$: C, 67.49; H, 8.09; N, 4.50. Found: C, 67.52; H, 8.09; N, 4.59.