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Regio- and stereocontrolled preparation of α-substituted phosphonocrotonate derivatives

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Abstract—Under suitable reaction conditions, monoalkylation of triethyl phosphonocrotonate **11** could be efficiently accomplished, leading to the preparation of α-substituted phosphonates **15**. The reaction is totally regioselective and completely (*E*)-selective. The novel phosphonocrotonate **19** underwent smooth Horner–Emmons condensation, producing a key-precursor for the synthesis of the middle core of the manzamine alkaloids. © 2002 Elsevier Science Ltd. All rights reserved.

Manzamine A **1** is a member of a growing family of unique indole alkaloids isolated by Higa and co-workers in 1986 from sponges of the genus *Haliclona* and *Pelina*.[1] The complex architectural framework of manzamine A **1**, coupled with its powerful biological activities[2]—antitumoral, antibacterial, cytotoxic and antimalarial—has stimulated considerable synthetic efforts towards its preparation,[3] culminating in 1998 with the first total synthesis of this natural product.[4] Our own interest in this area has prompted us to develop an efficient and flexible construction of the polycyclic middle core of the manzamines based upon a novel cascade anionic polycyclisation methodology (Fig. 1).[5] Thus, treatment of the substituted sorbate derivative **2**, easily available by Michael addition of the corresponding gramine to acrolein followed by a Horner–Emmons reaction, with KOBu^t smoothly afforded the tetracyclic system **3** in up to 55% yield.

Although this approach allowed us to assemble rapidly a variety of functionalised polycycles such as **3**, the introduction of the bridging 13-membered macrocyclic ring required unacceptably lengthy synthetic sequences. In order to circumvent this problem and maintain the high convergency of our approach, we envisioned that pentacycle **4** might be constructed from the macrocyclic amine **5** by a direct anionic polycyclisation (Fig. 2). Further disconnection of **5** revealed that it could be assembled readily from gramine **8**, acrolein **7** and the α-substituted phosphonocrotonate **9**. Subsequent cleavage of the C_3–C_4 bond generated commercially available triethyl phosphonocrotonate **11** and alkyne **10**.

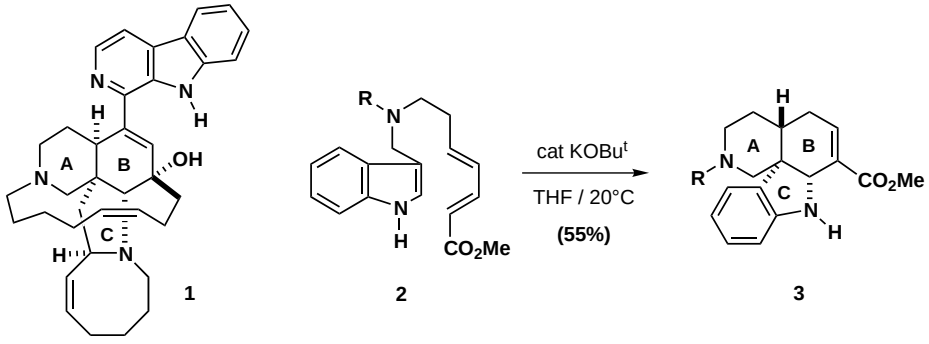

Figure 1.

Keywords: alkylation; phosphonocrotonate; polycyclisation; macrocycle; stereocontrol.
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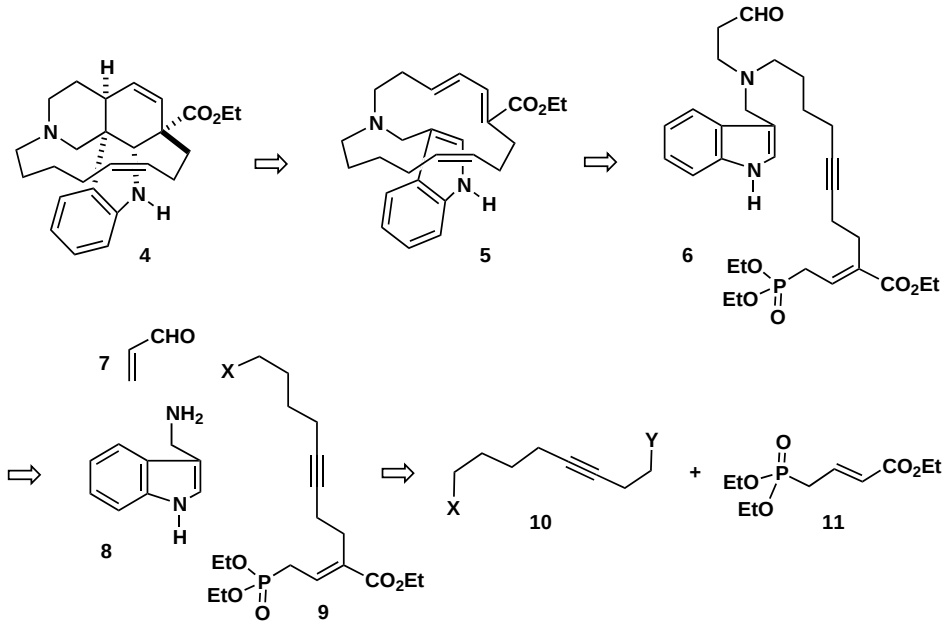


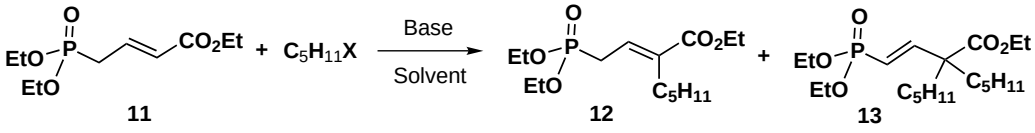
Figure 2.

Thus, a straightforward route to phosphonate **9**, and hence to macrocycle **5**, would involve the regioselective alkylation of **11** by **10**.[6]

Initial attempts at alkylating the anion derived from triethyl phosphonocrotonate **11** under usual conditions failed to deliver the desired substituted phosphorus reagent. Therefore, a more detailed study of the reaction conditions was conducted. Some selected results are collected in Table 1.

As can be seen from Table 1, alkylation of **11** using NaH as a base, in DMF, afforded a mixture of mono- and disubstituted adducts **12** and **13** in poor yields,

Table 1. Optimising the conditions for the alkylation of phosphonocrotonate **11**



Entry	X	Base	Solvent	T	**12** : **13**	Yield[(a)]
1	**OTs**	**NaH**	**DMF**	20°C	1 : 2	7%
2	**I**	**NaH**	**DMF**	20°C	2 : 1	25%
3	**OTf**	**LiHMDS**	**THF**	20°C	4 : 1	40%
4	**OTf**[(b)]	**LiHMDS**	**THF**	20°C	9 : 1	60%
5	**OTf**[(b)]	**LiHMDS**	**pentane**	0°C	10 : 1	58%
6	**OTf**[(b)]	**LiHMDS**	**Et_2O**	0°C	9 : 1	65%
7	**OTf**[(b)]	**NaHMDS**	**THF**	**-20°C**	**12 : 1**	**69%**

(a) All yields reported are for the pure, isolated mono-alkylation product **12**.
(b) Two equivalents of **11** were used in this reaction.

accompanied by a large amount of decomposition products (entries 1 and 2).[7] Screening various bases rapidly revealed that the use of LiHMDS minimised the decomposition of **11**, affording the mono- and dialkylated adducts **12** and **13** in reasonable yields (entry 3). Interestingly, the ratio of **12**:**13** depended strongly upon the nature of the leaving group, with the triflate affording the highest preference in favour of the monosubstituted product **12** (entries 1–3). Remarkably, no γ-adducts were produced under these reaction conditions.[8] Even more noteworthy is the observation that the monoalkylated phosphonate **12** was exclusively produced as the (*E*)-geometric isomer.[9]

Whilst the solvent and the temperature had little influence on the outcome of the alkylation (entries 4–6), the use of an excess of phosphonocrotonate (2 equiv. per alkylating agent) led, not only to improved yields, but also increased selectivity in favour of **12** (entries 3 and 4). Finally, an optimum was reached in this case using NaHMDS at −20°C (entry 7). Under these conditions, the desired pure adduct **12** was obtained in 69% yield, after purification (the ratio of **12**:**13** in the crude product = 12:1).

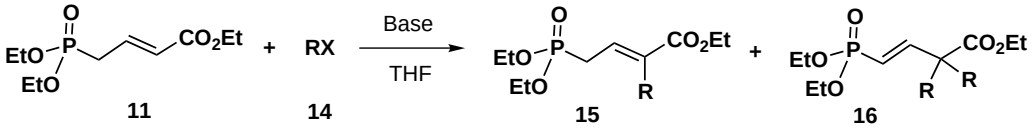
In order to delineate the scope of this protocol, we next applied it to a selection of alkylating agents. Some representative results are collected in Table 2.

As can be seen from Table 2, a range of primary and β-branched aliphatic substrates can be employed successfully in the alkylation of phosphonocrotonate **11** (entries 1–3). Allylic and benzylic halides are also good electrophiles (entries 4–6). However, the reaction is unsuccessful with secondary halides, such as isopropyl iodide (entry 7). It is interesting to note, that for some highly reactive alkylating agents, the use of LiHMDS rather than NaHMDS leads to better yields of **15** even though the ratio of crude **15**/**16** is slightly lower.[10]

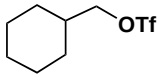
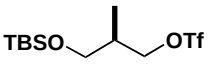
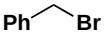
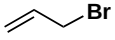
Having demonstrated the usefulness of this protocol for the preparation of a variety of substituted phosphonocrotonate derivatives, we next turned our attention to the synthesis of macrocyclic amine **5** (Fig. 3).

Alcohol **17**, available in large scale by the alkylation of 3-butyn-1-ol with 1-bromo-4-chlorobutane, was initially transformed into the corresponding triflate **18**, which reacted smoothly with the lithium anion of triethyl phosphonocrotonate **11**, affording the desired α-alkylated adduct **19** in 70% yield. Treatment of **19** with KOBu^t generated the corresponding enolate which underwent efficient Horner–Emmons[11] condensation with β-aminoaldehyde **21**, prepared quantitatively by the DBU-catalysed Michael addition of diallylamine **20** to acrolein **7**,[12] leading to the sorbate derivative **22** in an overall yield of 71%. Monodeallylation was accomplished quantitatively by selective replacement of one of the allyl substituents by trichloroethyl chloroformate and subsequent reductive work-up with Zn in AcOH.[13] Secondary amine **23** underwent smooth macrocyclisation in the presence of NaI and DIEA, affording **24** in 72% yield. Finally, deallylation followed by Mannich

Table 2. Monoalkylation of phosphonocrotonate **11**



11 **14** **15** **16**

Entry	RX	Base	t (min)	T	**15** : **16**	Yield[(a)]
1	CH_3I	**LiHMDS**	60	0°C	7 : 1	75%
2		**LiHMDS**	120	0°C	7 : 1	65%
3		**LiHMDS**	120	0°C	14 : 1	71%
4		**NaHMDS**	45	-20°C	5 : 1	63%
5		**NaHMDS**	60	-20°C	11 : 1	50%
6		**NaHMDS**	40	-20°C	6 : 1	73%
7	***i*-PrI**	**NaHMDS**	60	-20°C	---	3%

(a) All yields reported are for the pure, isolated mono-alkylation product **15**.

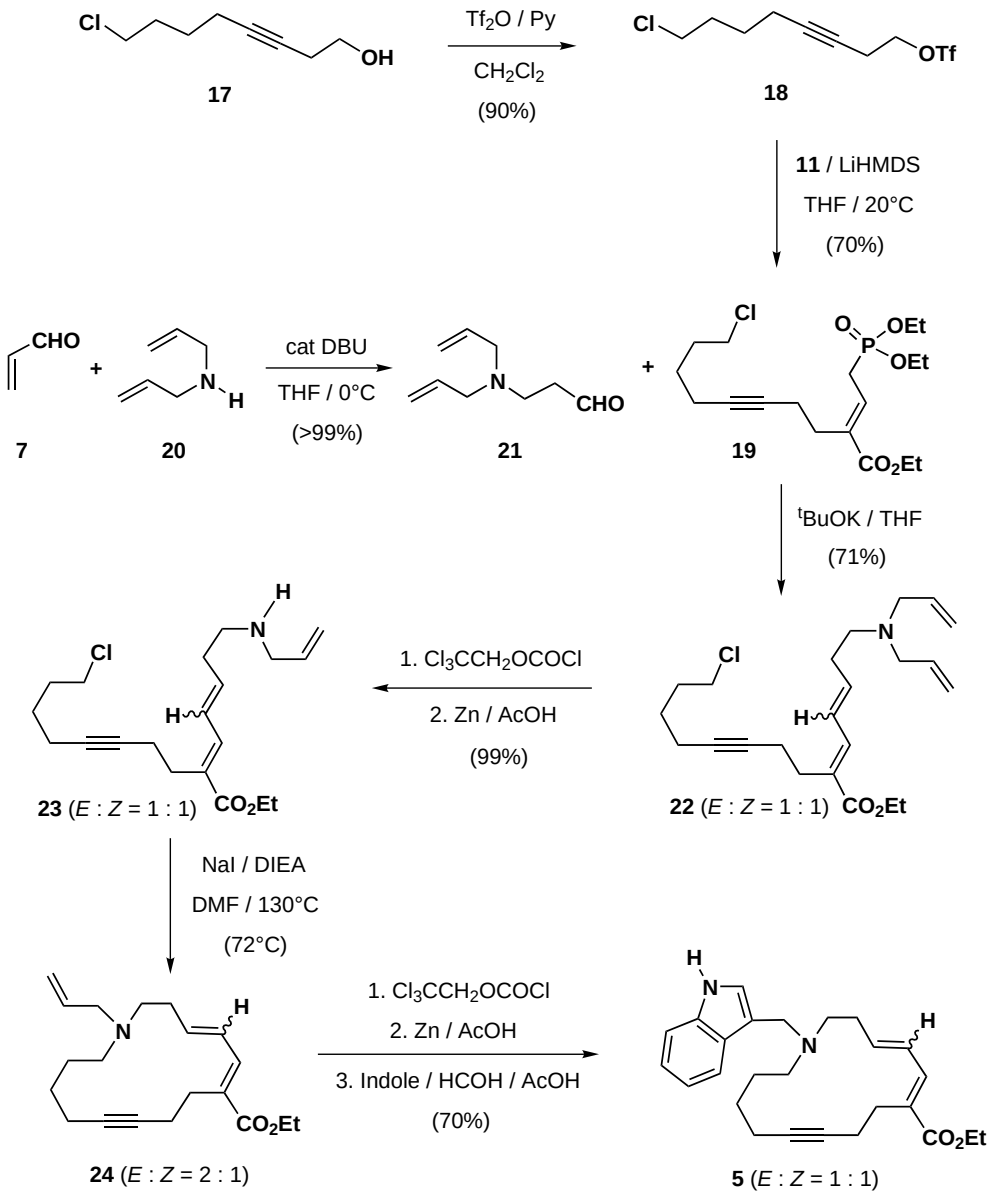


Figure 3.

condensation of the resulting amine with indole and formaldehyde,[14] delivered the desired macrocycle **5** in 70% overall yield, ready to undergo the anionic polycyclisation cascade.

In summary, we have demonstrated that under suitable reaction conditions, the monoalkylation of triethyl phosphonocrotonate could be efficiently accomplished, leading to the preparation of a range of α-substituted phosphonates.[15] The reaction is not only totally regioselective, affording solely the α-adducts, but also completely (*E*)-selective. These novel phosphonates undergo smooth Emmons–Horner condensation, producing functionalised sorbate derivatives. The synthetic usefulness of this methodology has been highlighted by the concise and efficient assembly of macrocyclic amine **5**, a key-precursor to the middle core of the manzamine alkaloids.

Current efforts are now being directed towards broadening the scope of this protocol and applying it to the total synthesis of manzamine A **1** and to other relevant natural products.

Acknowledgements

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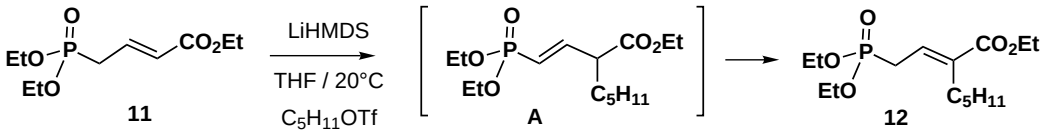

Figure 4.

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6. Much to our surprise, only one article describes the attempted methylation of phosphonocrotonate. However, mixtures of regio- and stereoisomers, contaminated by polyalkylation products, were obtained in modest yields. See: Kryshtal, G.; Zhdankina, G.; Serbryakov, E. *Russ. Chem. Bull.* **1997**, *46*, 1745.
7. Blank experiments performed by deprotonating **11** with NaH in DMF, at various temperatures, followed by quenching with H_2O revealed that rapid decomposition of the phosphonocrotonate anion occurred, leading to poor yields of recovered starting material.
8. The absence of γ-adducts probably reflects the greater steric hindrance of the phosphonate substituent as compared with the far less bulky and planar ester group.
9. This selectivity is probably the consequence of the preferential thermodynamic equilibration of the initial adduct **A** in favour of the better conjugated (*E*)-alkene **12**. It is interesting to note that **A** was never detected under the reaction conditions, thereby strongly suggesting that its transformation into **12** occurs rapidly and competitively with the alkylation of **11** (Fig. 4).
10. This is due to a slower decomposition of the lithium anion of phosphonate **11**, thereby producing a higher overall yield. Since the separation of the mono- and dialkylated adducts is trivial, it is often advantageous to aim for complete conversions with good selectivity rather than excellent selectivity with moderate yields.
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15. *Typical experimental procedure: synthesis of phosphonocrotonate **19***: To a cold (0°C) solution of triethyl phosphonocrotonate **11** (0.86 g, 3.44 mmol, 2 equiv.) dissolved in 20 mL of anhydrous THF and maintained under a positive pressure of argon, were added dropwise 2.62 mL (3.44 mmol, 2 equiv.) of a 1.3 M THF solution of LiHMDS. After stirring for 30 min at 0°C, the reaction mixture was brought to room temperature and a solution of triflate **18** (0.5 g, 1.7 mmol, 1 equiv.) in THF (2 mL) was added dropwise. After 90 min stirring at room temperature, 20 mL of a 10% aqueous solution of NH_4Cl were added and the organic layer was separated. The aqueous phase was washed three times with 50 mL of ether and the combined organic layers were dried over anhydrous $MgSO_4$. After filtration and removal of the solvents in vacuo, the crude product was purified by chromatography on silica gel (ethyl acetate:petroleum ether = 1:1) to afford the title compound **19** as a clear colourless oil (0.49 g, 73%). ^1H NMR (300 MHz, $CDCl_3$): 6.85 (dt, $J = 8.2$, 7 Hz, 1H), 4.15 (m, 6H), 3.55 (t, $J = 6.5$ Hz, 2H), 2.8 (dd, $J = 23.2$, 8.2 Hz, 2H), 2.55 (dt, $J = 7.4$, 2 Hz, 2H), 2.3 (tt, $J = 7.4$, 2.4 Hz, 2H), 2.15 (tt, $J = 4.6$, 2.4 Hz, 2H), 1.85 (m, 2H), 1.6 (m, 2H), 1.3 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.54 (C), 134.5 (d, $J = 14$ Hz, C), 131.6 (d, $J = 11$ Hz, CH), 79.85 (C), 79.65 (C), 62.22 (CH_2), 60.64 (CH_2), 44.45 (CH_2), 31.46 (CH_2), 28.86 (d, $J = 138$ Hz, CH_2), 26.26 (CH_2), 25.96 (CH_2), 18.22 (CH_2), 18.15 (CH_2), 16.25 (CH_3), 14.08 (CH_3). IR (cm^{-1}): 2982, 2937, 2908, 1710, 1647, 1255, 1164, 1025, 782. MS (CI, CH_4–N_2O): 393 (MH^+, Cl^{35}), 391 (M^+–1, Cl^{35}), 357 (M–Cl^{35}), 250.