Solid Phase Synthesis of Macrocycles by an Intramolecular Ketophosphonate Reaction. Synthesis of a (*dl*)-Muscone Library

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As part of our program directed at the development and application of solid phase synthetic technologies to complex molecule construction, we focused on the intramolecular ketophosphonate−aldehyde condensation. The intramolecular macrocyclization version of this reaction has proven to be a powerful method for the solution synthesis of complex natural products[1] and appeared to be ideally suited for cyclorelease,[2] in which a final step would involve simultaneous cyclization and release of the product from the solid support (Figure 1). Although polymer-bound phosphonates have been previously prepared[3] and used for intermolecular reactions to generate phosphonates and alkenes, to the best of our knowledge, their application to the synthesis of cyclic systems has not been reported. In this communication we wish to report the development of the solid-phase version of the intramolecular ketophosphonate−aldehyde reaction (Figure 1) and its application to the synthesis of macrocyclic lactones, the total synthesis of (*dl*)-muscone,[4] and the generation of a muscone library.

The practical implementation of the cyclorelease strategy presented in Figure 1 required an easy access to an appropriate polymer-supported methyl phosphonate. Scheme 1 summarizes a highly efficient, two-step process for the preparation of resin **3**, in which a linear spacer separates the polystyrene support from the reactive site of the phosphonate. Thus, Merrifield resin **1** was converted to resin **2** by reaction with 1,4-butanediol in the presence of NaH (99% yield)[5] and hence to phosphonate resin **3** by exposure to $CH_3P(O)(OCH_3)Cl$[6] (97% yield).[5]

Scheme 2 demonstrates the utilization of phosphonate resin **3** in the synthesis of macrocyclic lactones **11a** (18-membered) and **11b** (20-membered). Treatment of resin **3** with ^{n}BuLi, followed by addition of methyl ester **4** furnished **5**, which was desilylated by exposure to ^{n}Bu$_4$NF leading to **6**. The loading yield for **5** was determined by cleavage with K_2CO_3-18-Crown-6[7] and benzaldehyde, furnishing **12a** which was characterized and quantitated. Subsequent steps were monitored similarly (see Scheme 2 for more details). Condensation of alcohol **6** with carboxylic acids **7a** and **7b** yielded **8a** and **8b** from which **9a** and **9b** were respectively generated upon exposure to ^{n}Bu$_4$NF. Oxidation of the alcohols (**9a** and **9b**) with Dess−Martin reagent[8] led to the required precursors, aldehydes **10a** and **10b**, respectively. Finally, addition of K_2CO_3-18-Crown-6[7] to a suspension of **10a** and **10b** in toluene at 65 °C released macrocyclic systems **11a** and **11b** in 58 and 62% yield, respectively. Since only completed chains were able to enter the final step of the sequence, the purity of the final macrocyclic products was high (≥90% by ^{1}H NMR).

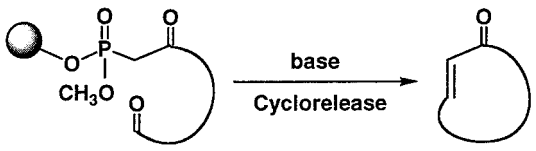
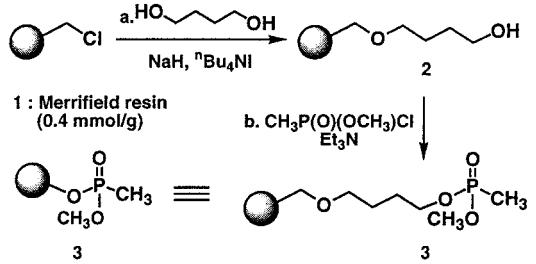


Figure 1. Cyclorelease of macrocycle with the ketophosphonate−aldehyde condensation reaction.

Scheme 1. Synthesis of Polymer-Supported Methylphosphonate[a]



[a] Reagents and conditions: (a) 1,4-butanediol (5.0 equiv), NaH (5.0 equiv), ^{n}Bu$_4$NI (0.1 equiv), DMF, 25 °C, 12 h, 99% yield;[5] (b) $CH_3P(O)(OCH_3)Cl$ (4.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 25 °C, 12 h, 97% yield.[5]

A conceptually different construction employing cross metathesis[9] was adopted for the synthesis of muscone and a small library of related macrocycles as shown in Figure 2. Radio frequency encoded Microkans[10,11] were utilized in a sort-pool combinatorial strategy. Thus, sorting and coupling of phosphonate SMART Microreactors **I** containing resin **3** with olefinic esters **A** proceeded, under the influence of ^{n}BuLi, to afford microreactors **II** (Figure 2). Further sorting and cross olefin metathesis of microreactors **II** with excess of alcohols **B** in the presence of $(PCy_3)_2Ru(=CHPh)Cl_2$ catalyst afforded olefins **III** as *E*:*Z* mixtures. The SMART Microreactors **III** were pooled

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(1) For early examples, see: (a) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069. (b) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010. (c) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Org. Chem.* **1979**, *44*, 4011. (d) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030. (e) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2808.

(2) For earlier examples of cyclorelease, see: (a) Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 10061. (b) Dewitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909. For carbon−carbon bond cyclorelease, see: (c) van Maarseveen, J. H.; den Hartog, J. A. J.; Engelen, V.; Finner, E.; Visser, G.; Kruse, C. G. *Tetrahedron Lett.* **1996**, *37*, 8249. (d) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1997**, *38*, 7143. (e) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268. (f) Gowravaram, M. R.; Gallop, M. A. *Tetrahedron Lett.* **1997**, *38*, 6973. (g) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem., Int. Ed.* **1998**. Submitted.

(3) (a) Cainelli, G.; Contento, M.; Manescalchi, F.; Regnoli, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2516. (b) Johnson, C. R.; Zhang, B. *Tetrahedron Lett.* **1995**, *36*, 9253. (c) Zhang, C.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 5457. (d) Cao. X.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 6073.

(4) For selected syntheses of muscone see: (a) Dowd, P.; Choi, S.-C. *Tetrahedron* **1992**, *48*, 4773 and references therein. (b) Takahashi, T.; Machida K.; Kido, Y.; Nagashima, K.; Ebata, S.; Doi, T. *Chem. Lett.* **1997**, *12*, 1291 and references therein. (c) Reference 1c.

(5) The corresponding resin was treated with an excess of Fmoc-Cl (ca. 5.0 equiv) in dichloromethane in the presence of pyridine (ca. 5.0 equiv) for 3 h. The reactive hydroxyl groups were photometrically determined from the amount of Fmoc chromophore released upon treatment of the Fmoc-resin with 10% Et_3N in CH_2Cl_2 (25 °C, 8 h).

(6) Balthazor, T. M.; Flores, A. R. *J. Org. Chem.* **1980**, *45*, 529.

(7) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954.

(8) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(9) Schuster, M.; Pernerstofer, J.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1979.

(10) For early work on radio frequency encoded combinatorial (REC) chemistry see: (a) Nicolaou, K. C.; Xiao, X.-Y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2289. (b) Moran E. J.; Sarshar, S.; Cargill, J. F.; Shahbaz, M. M.; Lio, A.; Mjalli, A. M. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 10787. For more recent work see: Nicolaou, K. C.; Vourloumis, D.; Li, T.; Pastor, J.; Winssinger, N.; He, Y.; Ninkovic, S.; Sarabia, F.; Vallberg, H.; Roschangar, F.; King, N. P.; Finlay, M. R. V.; Giannakakou, P.; Verdier-Pinard, P.; Hamel, E. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2097.

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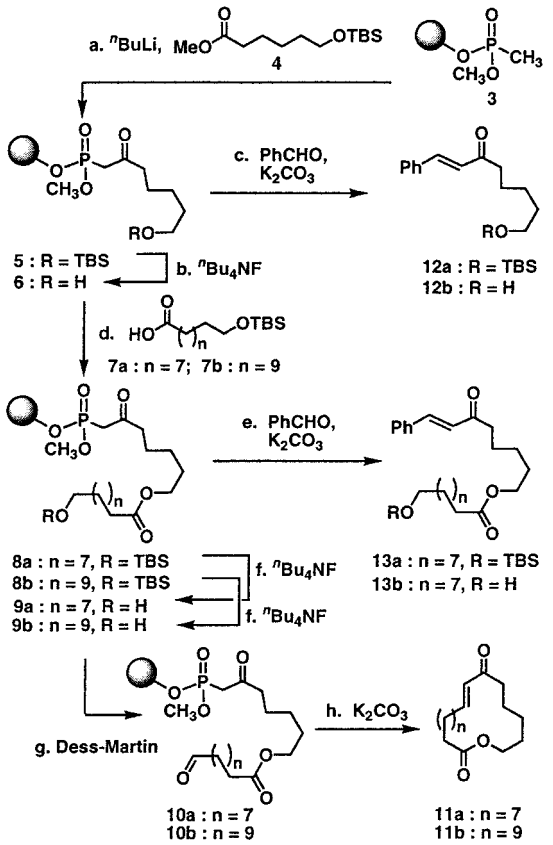
Scheme 2. Solid Phase Synthesis of Macrocyclic Lactones[a]



[a] Reagents and conditions: (a) ^{n}BuLi (1.6 M in hexanes, 1.2 equiv), THF, -20 °C, 10 min; then add **4** (4.0 equiv), −20 → 25 °C, 30 min; (b) TBAF (3.0 equiv), THF, 25 °C, 12 h, >95% yield;[5] (c) PhCHO (10.0 equiv), K_2CO_3 (5.0 equiv), 18-Crown-6 (5.0 equiv), toluene, 65 °C, 3 h, 68% from **1** for **12a**, and 87% from **6** for **12b** (*E*:*Z* ≥ 9:1); (d) **7a** or **7b** (2.0 equiv), DCC (2.2 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 12 h, >90%[5] for both; (e) PhCHO (10.0 equiv), K_2CO_3 (5.0 equiv), 18-Crown-6 (5.0 equiv), toluene, 65 °C, 3 h, 89% (**13a**; *E*:*Z* ≥ 9:1) and 92% (**13b**; *E*:*Z* ≥ 9:1), from **8a** and **9a**, respectively; (f) TBAF (3.0 equiv), THF, 25 °C, 12 h, >95% yield[5] in both cases; (g) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, 25 °C, 6 h, >90% yield;[5] (h) K_2CO_3 (5.0 equiv), 18-Crown-6 (5.0 equiv), toluene, 65 °C, 12 h, 58% (**11a**), 62% (**11b**) (*E*:*Z* ≥ 9:1). TBAF = tetrabutylammonium fluoride; 4-DMAP = 4-(dimethylamino)pyridine; DCC = 1,3-dicyclohexylcarbodiimide.

and oxidized with Dess−Martin reagent to give aldehydes **IV**. The aldehyde microreactors were sorted and treated with K_2CO_3-18-Crown-6,[7] causing smooth cyclorelease of macrocyclic enones **V** in good yield and high purity. Parallel solution phase chemistry completed the sequence. Thus, each one of these compounds was subjected to (a) cuprate addition to deliver a methyl or ^{n}-butyl group in a 1,4-fashion and (b) hydrogenation (H_2 5% Pd−C) to afford (*dl*)-muscone (**A** = **14a**; **B** = **15a**; **C** = **16a**) and modified muscones **VI**.

Among the advantages of the present cyclorelease method over its solution counterpart are (a) the ease of product isolation and no requisite for purification of intermediates, (b) the high purity of the final products due to the fact that incomplete substances do not enter the cyclorelease step, and (c) the avoidance of high dilution conditions and the absence of dimeric materials without compromising the yield of the product. The latter point is clearly evident from a comparison of the solid phase results for **V** (R^1=R^2=H, 65% yield, see Supporting Information) with those for the corresponding solution reaction in which 15−20% yield of the dimeric product was obtained even under high dilution conditions.[1c]

The described chemistry adds the powerful intramolecular ketophosphonate−aldehyde condensation reaction to the solid phase reaction library and demonstrates its power in the synthesis of natural products and combinatorial compound libraries. The construction of the muscone library in particular may point to new vistas in the perfumery industry while the general strategies proposed herein may find wider applications in drug discovery and other research laboratories.

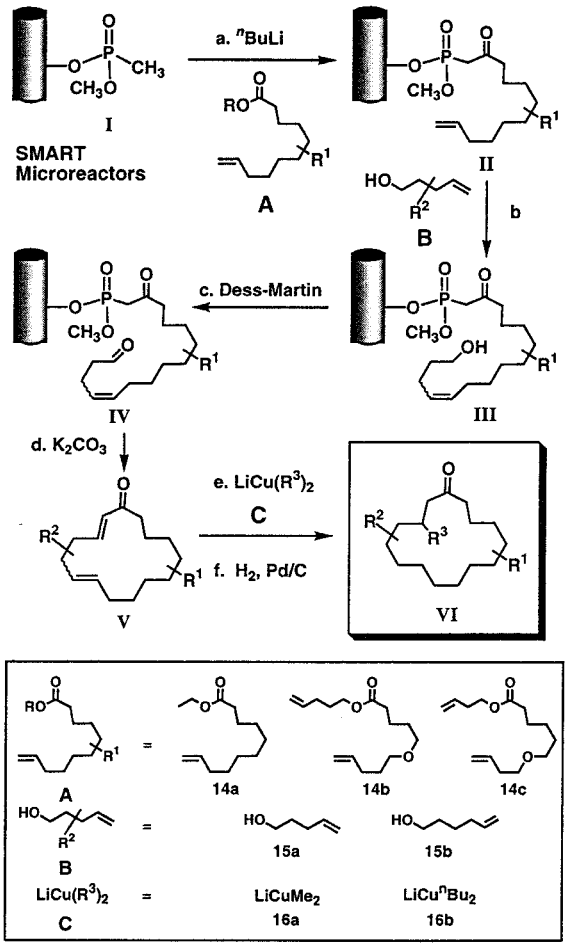


Figure 2. Solid phase combinatorial synthesis of a muscone library. Reagents and conditions: (a) 1. Sort SMART Microreactors (with an IRORI Accutag-100 apparatus); 2. ^{n}BuLi (1.6 M in hexanes, 1.2 equiv), THF, −20 °C, 10 min; then add **A** (4.0 equiv), −20 → 25 °C, 30 min; 3. Sort; (b) 1. **B** (5.0 equiv), $(PCy_3)_2Ru(=CHPh)Cl_2$ (0.2 equiv), C_6H_6, 25 °C, 48 h, 60−70% from Merrifield resin;[5] 2. Pool; (c) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, 25 °C, 6 h, >90% yield;[5] (d) 1. Sorting of individual SMART Microreactors; 2. K_2CO_3 (5.0 equiv), 18-Crown-6 (5.0 equiv), benzene, 65 °C, 12 h, 35−65% yield; (e) **C** (1.2 equiv), Et_2O, 0 °C, 1 h, >90%; (f) H_2, 5% Pd−C, MeOH, 25 °C, 2 h, 75−95%.

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Supporting Information Available: Experimental procedures for the synthesis of compounds **1**−**14** and **II**−**VI** and selected physical data (^{1}H, ^{13}C, IR, HRMS) for compounds **4**, **7ab**, **11ab**, **12ab**, **13ab**, **14a**−**c**, **VI** (12 compounds) and **V** (6 compounds) (27 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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