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Macrocyclization of terminal bis-allylic chlorides via an intramolecular gem-dialkylation of malononitrile or methyl cyanoacetate

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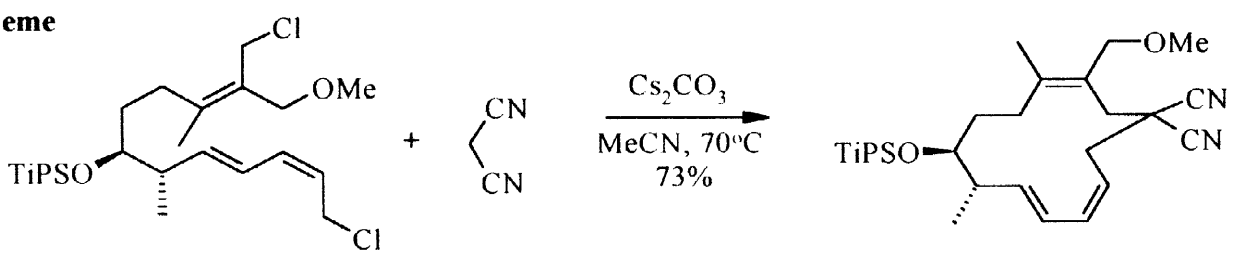
Abstract

A procedure is described for the stereospecific synthesis of 13-membered trienic macrocycles from suitable acyclic bis-allylic chlorides via an intramolecular gem-dialkylation of malononitrile or methyl cyanoacetate.

Keywords: Alkylation, Coupling reagents, Cyano Compounds, Macrocycles.

In the course of our studies on the transannular Diels-Alder (TADA) reaction, we needed to generate 13-membered macrocycles with appropriately positionned dienes and dienophiles. To obtain these synthetic intermediates, a stepwise alkylation of malononitrile or methyl cyanoacetate as connectors with terminal allylic chlorides was achieved. The latter were prepared from the corresponding properly protected allylic alcohols. However, with these connectors, it is known that dialkylation is always competitive [1,2]. This was apparent in our system, as shown by the formation of 3% of dialkylated connector even with its 30-fold excess. The second alkylation is particularly fast in short chain intramolecular cases to allow practical small ring annulations [3]. These information suggested that large ring annulations should be tested(**Scheme**).

Scheme



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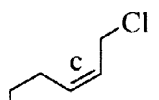
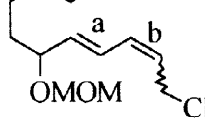
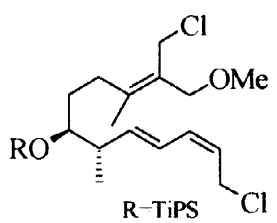
Indeed, good yields of 13-membered trienic macrocycles were obtained when these connectors were subjected to alkylation with α,ω-bis-allylic chlorides (**Table**) [4,5]. These reactions are remarkable in the sense that they override a multitude of competing reactions such as intermolecular dialkylation, S_N2' displacement and dehydrohalogenation [2]. Moreover, the substrates require fewer steps to synthetize as functional groups at both ends can be developed in parallel. The yields follow the general trend favoring *cis*-double bonds in the substrate [6]. In conclusion, the described methodology affords the necessary macrocycles for the TADA reaction in good yield.

Table Macrocyclization trials[a]

Entry	Substrate	[abc][b]	Connector	Solvent	Temp. °C	Add. time h	Yield[c] %
1		[TCC]	NC$\diagdown\!\diagup$$CO_2Me$	THF/DMF (2:1)	78	10	79
2		[TCC]	NC$\diagdown\!\diagup$CN	Acetonitrile	78	10	>50
3		[TTC]	NC$\diagdown\!\diagup$CN	Acetonitrile	78	15	55
4		[TCC]	NC$\diagdown\!\diagup$CN	Acetonitrile	70	10	73
5		[TCC]	NC$\diagdown\!\diagup$$CO_2Me$	Acetonitrile	70	10	53

[a] The substrate was added to a suspension of Cs_2CO_3 (5 eq.) under high dilution conditions (c_{final}~2 mM)[5].
[b] Letters in brackets denote double bonds stereochemistry (*cis*, *trans*) of the substrate and the macrocycle.
[c] Macrocycles (entries 1 and 5) are a mixture (1:1) of diastereoisomers.

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References and Notes:

[1] Stowell JC. *Carbanions in Organic Synthesis*, First Edition, New York, John Wiley, **1979**:210-212.

[2] Cope AC, Holmes HL, House HO. *The Alkylation of Esters and Nitriles. Organic Reactions*. New York: John Wiley, **1957**;*9*:107-331.

[3] Campaigne E, Forsch RA. *J. Org. Chem.* **1978**;*43*:1044-1050.

[4] The choice of base and solvents can favor dialkylation see:
Ono N, Yoshimura T, Saito T, Tamura R, Tanikaga R, Kaji A. *Bull. Chem. Soc. Jpn* **1979**;*52*:1716-1719.

[5] A solution of dichloride (entry 1, 720 mg , 2.25 mmol) and methyl cyanoacetate (298 µL, 3.38 mmol) in THF (20 mL) was added with a syringe pump in 10 h to a suspension of Cs_2CO_3 (10 g, 30.70 mmol) in THF/DMF (800 mL, 2:1, C_{final}=2.7 mM) at 78°C under nitrogen. The DMF was purged with nitrogen for 1 h before use. The solution was vigorously stirred for an additionnal hour after addition, then cooled and filtered. The crude was purified by flash chromatography (hexanes/ether 8:2) to yield the pure macrocycle as an oil (568 mg, 79%).
IR (cm^{-1}): 2934, 2248, 1747, 1440, 1219. ^{1}H-NMR ($CDCl_3$, ppm): 6.45-6.25 (2H, m, *J*=15.2, HC=C<u>H</u>-<u>H</u>C=CH), 5.90 (1H, t, *J*=15.0 and 5.8 Hz, CH-<u>H</u>C=CH), 5.62-5.5 (1H, m, CH_2CH_2<u>H</u>C=CH), 5.42-5.20 (2H, m, 2 x HC=C<u>H</u>CH_2C), 4.62 (2H, qd, *J*=9.7 and 1.7Hz, O<u>C</u>H_2O), 4.18 (1H, q, *J*=7.8 Hz, C<u>H</u>(OMOM)), 3.86 (3H, s, O<u>C</u>H_3), 3.37 (3H, s, CO_2<u>C</u>H_3), 2.8-2.43 (4H, m, 2 x CH=CH-C<u>H</u>$_2$C), 2.22-1.30 (6H, m, other CH_2). HR-MS: Calculated: 319.1783 found: 319.1789 ± 0.0010.

[6] In a *trans-trans-trans* system, a 10% yield of this macrocyclization is still competitive with the stepwise intermolecular bis-alkylation. Due to the formation of TADA products during the macrocyclization the characterization is difficult.