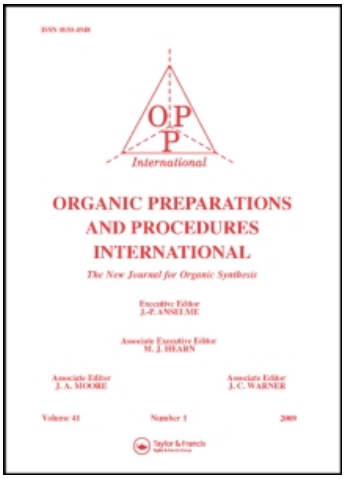


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

MACROCYCLE SYNTHESES: CYCLIC KETONES, KETOALKENES, DIKETONES AND DIENES OF RING SIZE C_{21} TO C_{26}

Malcolm D. E. Forbes[a]; Yi Dang[a]
[a] Department of Chemistry, Venable and Kenan Laboratories, University of North Carolina, Chapel Hill, NC

To cite this Article Forbes, Malcolm D. E. and Dang, Yi(1993) 'MACROCYCLE SYNTHESES: CYCLIC KETONES, KETOALKENES, DIKETONES AND DIENES OF RING SIZE C_{21} TO C_{26}', Organic Preparations and Procedures International, 25: 3, 309 — 314
To link to this Article: DOI: 10.1080/00304949309457965
URL: http://dx.doi.org/10.1080/00304949309457965

ORGANIC PREPARATIONS AND PROCEDURES INT., 25 (3), 309-314 (1993)

MACROCYCLE SYNTHESES: CYCLIC KETONES, KETOALKENES, DIKETONES AND DIENES OF RING SIZE C_{21} TO C_{26}

Malcolm D. E. Forbes* and Yi Dang

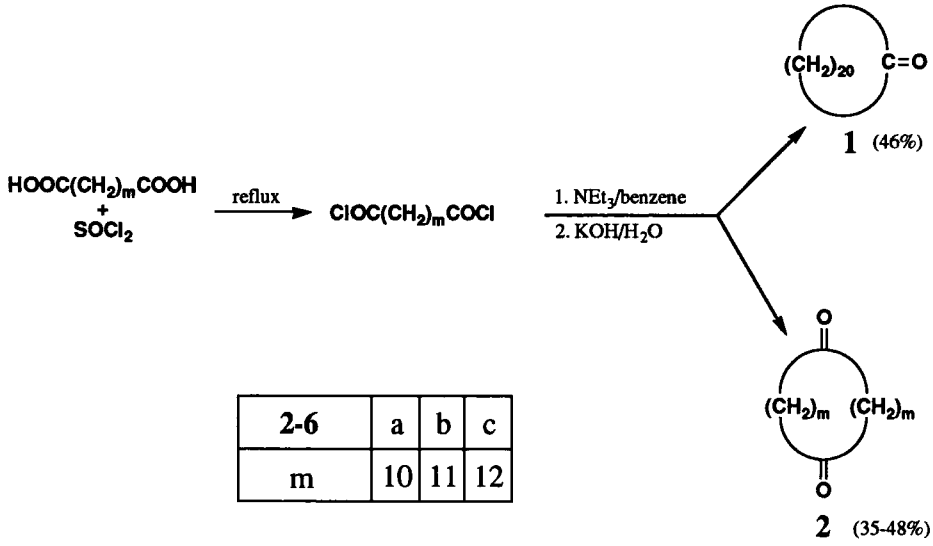
Department of Chemistry, Venable and Kenan Laboratories
University of North Carolina, Chapel Hill, NC 27599-3290

Organic macrocycles (> C_7) are interesting from both theoretical and practical perspectives,[1] and are highly sought after synthetic targets.[2,3] Depending on ring size, they may show novel transannular interactions,[4-6] complicated conformational dynamics,[7] or interesting photochemical properties.[8] Also, many saturated and unsaturated macrocyclic ketones are of particular interest to the fragrance industry.[9] As part of an ongoing research project studying reactive intermediates produced in the photoexcitation of cyclic ketones,[10] we have synthesized several mono- and difunctional rings ranging in size from C_{21} to C_{26}.

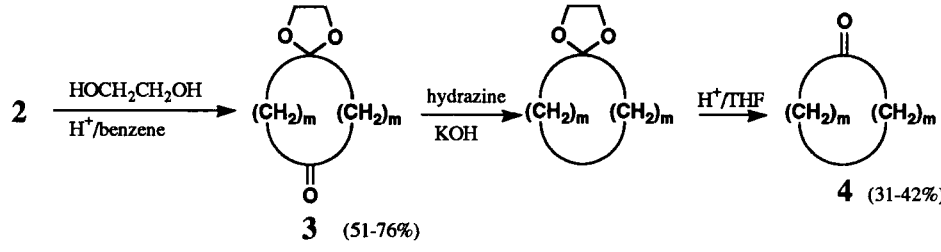
The macrocyclization technique used *viz.* the dimerization of linear dicarboxylic acid chlorides originally reported by Blomquist[11] has been extensively used by Marshall and coworkers in the synthesis of "betweenanenes."[12] We have further manipulated the resulting diones from the ring closure reaction to prepare saturated and unsaturated cyclic monoketones, cyclodienes, and cycloalkanes in reasonable yields and high purity. The present paper describes detailed experimental procedures and lists the physical properties of these interesting molecules. The unsaturated ketones reported are unknown, and the syntheses of diketones and dienes represent an improvement of previous methods in terms of facility and availability of starting materials.

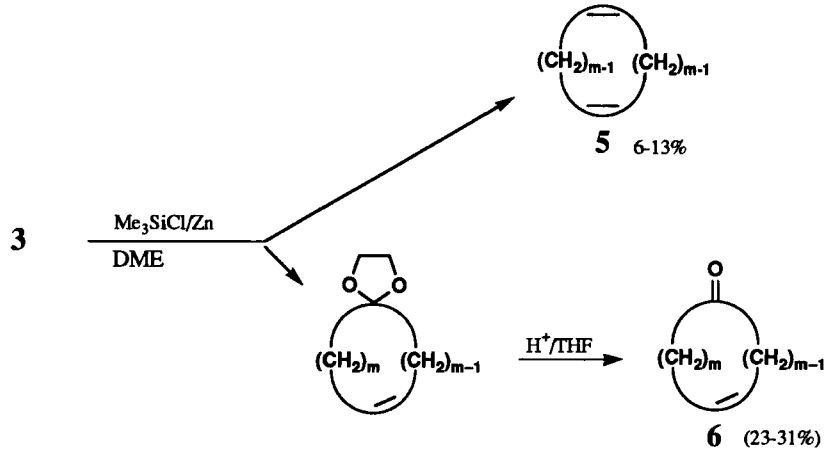
The reaction sequence is outlined below. The macrocyclic diones **2** were prepared in 35-48% yield from the corresponding diacids. Monoketalization of these ketones was straightforward using ethylene glycol in the presence of an acid catalyst. Monoketals **3** were converted to ketal-olefins by treatment with an excess of chlorotrimethylsilane and zinc in a convenient one-step reaction.[13,14] This method was improved to give better yields by using a higher boiling solvent (1,2-dimethoxyethane) at reflux temperature, and a longer reaction time. Cyclic dienes **5** were obtained as by-products in some cases, and these were isolated as mixtures of the three possible isomers.[15] Deprotection of the ketal-alkenes to the ketoalkenes **6** was performed using acid hydrolysis. The unsaturated ketones were mixtures of *cis* and *trans* isomers (approximately 1:1 ratio), determined by GC/MS and NMR. Wolff-Kishner reduction of the monoketals afforded the saturated monoketals, which upon acid hydrolysis in THF gave the saturated cyclic monoketones **4**.[16] Cyclic diones and cycloalkanes were sometimes

recovered as minor products after column chromatography.



2-6	a	b	c
m	10	11	12





In the attempted cyclization of the 1,22-dicarboxylic acid chloride to a C_{42} ring, we expected the reaction to proceed as for the shorter chain length diacid chlorides by intermolecular dimerization to the larger ring; instead, we observed an intramolecular cyclization in 46% yield to a C_{21} monoketone ring **1**. This reaction is analogous to the Dieckmann condensation of a linear diester.[17] This result was difficult to confirm since physical data are very similar for the monomer and dimer. The conversion of ketal **3** to the cyclic alkene **5** produced only two isomers detectable by GC/MS instead of three expected for the cyclic diene, and these were of the correct mass for the *cis* and *trans* isomers of the cyclic monoalkene. Also, any unsaturated ketone **6** could not be isolated, and the GC retention time of the saturated ketone **4** was significantly less than that of the C_{22} and larger rings. In our low resolution GC/MS it was not possible to elute the C_{42} ring, but traces of it could be observed in the final product mixture using high resolution FAB mass spectrometery. The intramolecular reaction is a somewhat surprising result, and suggests a strategy for the synthesis of odd-numbered macrocycles which may be difficult to make via other routes.

EXPERIMENTAL SECTION

All NMR spectra were recorded on a Varian XL400 or a Bruker AC200 spectrometer in deuterated chloroform, and FTIR spectroscopy was conducted in CCl_4 solution on a Mattson Polaris spectrometer. UV/VIS spectra were measured on a Perkin Elmer Lambda 6 spectrophotometer, and GC/MS spectra were collected on a Hewlett-Packard 5890 instrument equipped with a 5971 mass spectrometer detector. Elemental Analyses were performed by Atlantic Microlabs, Inc., Georgia. All melting points were taken on a Fisher-John melting point apparatus and are uncorrected.

All dicarboxylic acid chlorides were prepared by refluxing the corresponding acids (Aldrich) for 3 hrs in excess thionyl chloride, which was removed in vacuo after completion of the reaction. The acid chlorides were used for cyclization without further purification. For the synthesis of macrocyclic-α,ω-diones, the original procedure as described by Blomquist[11] was followed exactly. The diones were purified before the next step by column chromatography or recrystallization. Monoketone **1** was obtained under identical reaction conditions for the dimerization reactions, starting from 1,22-docosanedioic acid dichloride. Physical constants for all new compounds are listed in Table 1, and the IR, ^1H and ^{13}C NMR data are listed in Table 2.

Macrocyclic Monoketals (3). Typical Procedure.- A mixture of 1,12-cyclodocosanedione **2a** (20 mmol, 6.7 g) and ethylene glycol (22 mmol, 1.4 g) in benzene (300 mL) was refluxed overnight in the presence of catalytic amount of *p*-toluenesulfonic acid monohydrate using a Dean-Stark trap. The reaction was quenched with 5% aqueous sodium bicarbonate (200 mL). The aqueous layer was extracted with ether (2 x 200 mL) and the organic layers combined and washed with water (2 x 400 mL) and brine (1 x 400 mL). Purification by column chromatography on silica gel (200-400 mesh) eluted with hexanes/benzene gave the monoketal **3a** (5.8 g, 76 %).

Macrocyclic Keto-alkenes (6). Typical Procedure.- A mixture of the monoketal of 1,12-cyclodocosanedione (13.2 mmol, 5g) and chlorotrimethyl-silane (70.9 mmol, 9 mL) in

Table 1. Melting Points and Elemental Analyses

Cmpd	mp (°C)	Solvent	λ^{a}_{max}	ε	Elemental Analysis (Found) C	H
1	39	benzene/pet. ether	280[b]	105	81.74 (81.78)	13.07 (13.00)
4a	40	EtOAc/pet. ether	258[b] 278	33 31	81.91 (82.14)	13.13 (13.06)[d]
4b	34	EtOAc/pet. ether	279[b]	24	82.21 (82.11)	13.22 (13.21)
4c	41	EtOAc/pet. ether	236[b] 280	22 22	82.46 (82.67)	13.31 (13.44)
5a	oil	–	198[c] 235	710 129	86.73 (86.56)	13.26 (13.41)
5b	oil	–	198[c] 237	765 115	86.64 (86.61)	13.36 (13.26)
5c	56	hexanes	200[c] 228	1250 473	86.56 (86.61)	13.44 (13.37)
6a	oil	–	234[b] 277	51 15	82.43 (82.35)	12.58 (12.47)
6b	32	benzene/hexanes	232[b] 279	124 24	82.69 (82.56)	12.72 (12.63)
6c	49	EtOAc/pet. ether	225[b] 279	161 25	82.90 (82.60)	12.84 (12.89)

a) λ in nm; b) Solvent: methanol; c) Solvent: hexane; d) Single run.

dimethoxyethane (80 mL) was mixed with zinc dust (153.8 mmol, 10 g), and the mixture refluxed with stirring for four days. After cooling and filtration, the residue was dissolved in diethyl ether (300 mL) and washed with saturated aqueous sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate, and evaporated to give the crude product. NMR and IR indicated the formation of the double bond and the removal of the carbonyl group. The solid was hydrolyzed by refluxing with 10% aqueous hydrochloric acid (20 mL) in tetrahydrofuran (150 mL) for 12 hrs. After cooling and reduction of the solvent to a volume of 25 mL under vacuum, the remaining solution was partitioned between water and ethyl acetate. The organic phase was separated and washed with saturated aqueous sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate, and concentrated under vacuum. The residue was chromatographed on silica gel (200-400 mesh) eluted with hexanes/benzene/ether. The first fraction (hexanes) gave 1,12-cyclodocosanediene **5a** as an oil (0.5 g, 13%). The keto-alkene **6a** (hexanes, 20-50% benzene) was a colorless oil (1.3 g, 31%), and finally the dione **2a** (0.9 g, 20%) was obtained with benzene/ether (5:1).

Table 2. IR and NMR Data for Compounds **1**, **4-6**

Product	IR(CCl_4) υ (cm^{-1})	^1H NMR ($CDCl_3$) δ (ppm)	^{13}C NMR ($CDCl_3$) δ (ppm)
1	2928, 2855, 1715 (CO), 1551, 1252, 1221	2.22 (4H), 1.44 (4H), 1.13 (32H)	211.0 (CO), 42.2, 28.2, 23.7
4a	2930, 2858, 1715 (CO), 1549, 1260	2.36 (4H), 1.57 (4H), 1.25 (34H)	212.0 (CO), 42.4, 28.1, 23.8
4b	2928, 2855, 1715 (CO), 1551, 1462, 1254	2.38 (4H), 1.58 (4H), 1.26 (38H)	212.0 (CO), 42.4, 28.6, 23.8
4c	2928, 2855, 1715 (CO), 1549, 1254, 1217	2.38 (4H), 1.58 (4H), 1.27 (42H)	212.0 (CO), 42.6, 28.9, 23.8
5a	2930, 2855, 1551, 1263, 1217, 1005	5.36 (4H), 2.02 (8H), 1.28 (28H)	130.8, 130.0, 27.0-32.2
5b	2928, 2855, 1551, 1250, 1217, 1005	5.35 (4H), 2.01 (8H), 1.27 (32H)	130.7, 130.0, 26.8-32.2
5c	2960, 1548, 1431, 1250, 1005, 982	5.35 (4H), 2.01 (8H), 1.27 (32H)	130.7, 130.0, 26.9-32.2
6a	2926, 2855, 1715 (CO), 1549, 1462, 1256	5.26 (2H), 2.33 (4H), 1.95 (4H), 1.54 (4H), 1.20 (26H)	211.9 (CO), 130.6, 129.9,42.2, 32.1, 28.8, 26.8, 23.8
6b	2928, 2855, 1715 (CO), 1549, 1252, 1005	5.32 (2H), 2.36 (4H), 1.97 (4H), 1.57 (4H), 1.24 (30H)	212.1 (CO), 130.6, 130.0,42.3, 32.1, 28.8, 26.8, 23.8
6c	2930, 2855, 1715 (CO), 1551, 1254, 1217	5.36 (2H), 2.38 (4H), 2.00 (4H), 1.60 (4H), 1.25 (34H)	212.2 (CO), 130.6, 130.0,42.3, 32.2, 28.8, 26.9, 23.9

Saturated Macrocyclic Ketones (4). Typical Procedure.- The procedure given is for the synthesis of cyclotetracosanone **4b**. To a solution of the monoketal of 1,13-cyclotetracosanedione **3b** (1.4 g, 3.43 mmol) in triethylene glycol (50 mL) was added 55% hydrazine hydrate (5.6 mL) and potassium hydroxide (2.4 g, 142.8 mmol). This mixture was heated at reflux for 5 hrs in an oil bath at 160°C. The condenser was removed and the bath temperature raised to 195°C, where it was maintained for 4 hrs. The mixture was then cooled and partitioned between benzene (200 mL) and 10% aqueous hydrochloric acid (200 mL). The organic layer was separated and washed with 10% hydrochloric acid (3 x 50 mL), water (50 mL) and saturated sodium bicarbonate (100 mL). After drying over magnesium sulfate, the solvent was removed to give a yellow solid. Deprotection to the ketone was carried out as described for the unsaturated ketones. Three products were separated by column chromatography: cyclotetracosane was obtained as a waxy solid (0.3 g, 26%) with petroleum ether (35-60°C), cyclotetracosanone as white solid (0.5 g, 42%) with petroleum ether/benzene (6:5), and 1,13-cyclote-

tracosanedione as crystalline solid (0.2 g, 17 %) with benzene/diethyl ether (5:1).

Acknowledgments.- We thank the National Science Foundation for support of this work through grant CHE-9200917. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support through grant ACS PRF 23636-G,4. We thank G. R. Schulz for assistance in the preparation of the manuscript.

REFERENCES

1. W. C. Still and I. Galynker, *Tetrahedron*, **37**, 3981 (1981).

2. P. Dowd and S.-C. Choi, *ibid*, **48**, 4773 (1992).

3. H. Hesse, *Ring Enlargement in Organic Chemistry*, VCH: Weinheim, 1991.

4. R. Bishop, *Australian J. Chem.*, **37**, 319 (1984).

5. T. J. Lewis, S. J. Rettig, J. R. Scheffer, J. Trotter and F. Wireko, *J. Am. Chem. Soc.*, **112**, 3679 (1990).

6. T. J. Lewis, S. J. Rettig, J. R. Scheffer and J. Trotter, *ibid.*, **113**, 8180 (1991).

7. V. L. Shannon, H. L. Strauss, R. G. Snyder, C. A. Ellinger and W. L. Mattice, *ibid.*, **111**, 1947 (1989).

8. K. Matsui, T. Mori and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **44**, 3440 (1971).

9. P. Z. Bedoukian, *Perfumery and Flavoring Synthetics*, Allured Publishing, Wheaton, Illinois, USA, 1986, p. 301 ff.

10. M. D. E. Forbes, K. E. Dukes, T. L. Myers, H. D. Maynard, C. S. Breivogel and H. B. Jaspan, *J. Phys. Chem.*, **95**, 10547 (1991).

11. A. T. Blomquist, J. Prayer, J. Wolinsky, *J. Am. Chem. Soc.*, **77**, 1804 (1955).

12. J. A. Marshall, M. Constantino and T. H. Black, *Synth. Commun.*, **10**, 767 (1980).

13. P. Hodge and M. N. Khan, *J. Chem. Soc., Perkin I*, 809 (**1975**).

14. W. B. Motherwell, *Chem. Commun.*, 935 (**1973**).

15. H. J. Bestmann and H. Pfüller, *Angew. Chem. Internat. Ed.*, **11**, 508 (1972).

16. K. Ziegler and W. Hechelhammer, *Ann.*, **528**, 114 (1937).

17. N. J. Leonard and C. W. Schimelpfenig, Jr., *J. Org. Chem.*, **23**, 1708 (1958).

(Received January 19, 1993; in revised form March 1, 1993)