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Desymmetrization of Cyclic Anhydrides Using Dihydroxy Compounds: Selective Synthesis of Macrocyclic Tetralactones

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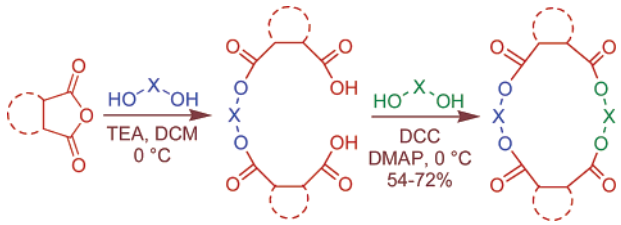
ABSTRACT



The desymmetrization of cyclic anhydrides is carried out using dihydroxy compounds. A mild route to synthesize fused saturated/unsaturated macrocyclic tetralactones with different ring sizes (20–34) having a wide variety of spacers is described. The structure is confirmed by the representative single-crystal X-ray analysis. The multiple reduction of unsaturated macrocyclic tetralactones is also illustrated. This method is mild, selective, and efficient and achieves high yield.

Great attention has been focused on the synthesis of macrolides, particularly dilactones, due to their biological properties, ability to form complexes and ion carriers, and application in the perfume industry.[1] Since Pederson's discovery of macrocyclic polyether (crown) compounds, extensive research has been carried out toward their synthesis and ion selectivity.[2] Many researchers have been involved in the synthesis of dilactones because of their potential importance in ion transports.[3] However, only a limited number of methods for the preparation of macrocylcic dilactones are currently available. These methods involve the reaction of the dicesium salts of acids with dibromides,[4] reaction of acid chlorides with glycols,[5] condensation of dipotassium salt of acids with dibromides,[6] condensation of dicarboxylic acids with benzyl bromides,[7] reaction of acid chlorides with ω-bromo alcohols,[8] condensation of diacid chlorides with diols under phase-transfer catalysis,[9] cyclization of sulfonium salts in the presence of cesium carbonate,[10] or the reaction assisted by alkaline metals.[11] Recently,

(1) Bradshaw, J. S.; Maas, G. E.; Izatt, R. M.; Christensen, J. J. *Chem. Rev.* **1979**, *79*, 37.
(2) (a) Bogdanova, A.; Perkovic, M. W.; Popik, V. V. *J. Org. Chem.* **2005**, *70*, 9867. (b) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.
(3) (a) Griesbeck, A. G.; Henz, A.; Hirt, J. *Synthesis* **1996**, 1261. (b) Masamune, S.; Bates, S. G.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (c) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.
(4) Piepers, O.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1978**, 383.
(5) Asay, R. E.; Bradshaw, J. S.; Nielsen, S. F.; Thompson, M. D.; Snow, J. W.; Masihdas, D. R. K.; Izatt, R. M.; Christensen, J. J. *J. Heterocycl. Chem.* **1977**, *14*, 85.
(6) (a) Drewes, S. E.; Coleman, P. C.*J. Chem. Soc., Perkin Trans. 1* **1972**, 2148. (b) Drewes, S. E.; Riphagen, B. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1908.
(7) Drewes, S. E.; Riphagen, B. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 323.
(8) Samat, A.; Bibout, M. E. M.; Elguero, J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1717.
(9) (a) Zhou, Z.; Schuster, D. I.; Wilson, S. R. *J. Org. Chem.* **2003**, *68*, 7612. (b) Singh, P.; Kumar, M.; Singh, H. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1987**, *26*, 64. (c) Singh, H.; Kumar, M.; Singh, P. *J. Chem. Res., Miniprint* **1989**, *4*, 675.
(10) Nakamura, T.; Matsuyama, H.; Kamigata, N.; Iyoda, M. *J. Org. Chem.* **1992**, *57*, 3783.
(11) Takahashi, S.; Souma, K.; Hashimoto, R.; Koshino, H.; Nakata, T. *J. Org. Chem.* **2004**, *69*, 4509.

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synthesis of dilactones was also reported through lipase catalysis[12] or photochemical acylation.[13] Even though methods available in the literature provide a mixture of dilactones and tetralactones, the reactions give low yields and require drastic conditions. Thus, in this paper, we report a new high-yielding, selective method to synthesize macrocyclic tetralactones having various spacers/ring sizes via dicyclohexylcarbodiimide (DCC)-mediated double esterification of dicarboxylic acids.

Toward the objective to synthesize new macrocycles, we initially proposed performing the desymmetrization[14] of cyclic anhydrides (Figure 1) in the presence of dihydroxy

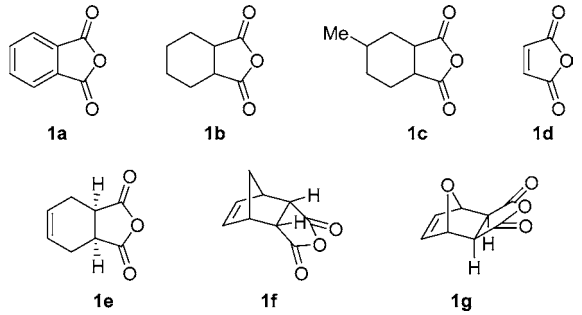


Figure 1. Anhydrides used for the desymmetrization reactions.

compounds. Therefore, an excess amount of phthalic anhydride **1a** was reacted with 1 equiv of tetra(ethylene glycol) in the presence of triethylamine to furnish the corresponding dicarboxylic acid **3a** in 90% yield (Scheme 1, Table 1). The product was undoubtedly confirmed on the basis of the spectral data. This interesting result encouraged us to investigate this reaction with various dihydroxy compounds. Toward this end, the anhydride **1a** was reacted with several diols such as tri(ethylene glycol) and 1,2-benzenedimethanol to afford the respective products **3b**,**c** in good yield.

Scheme 1

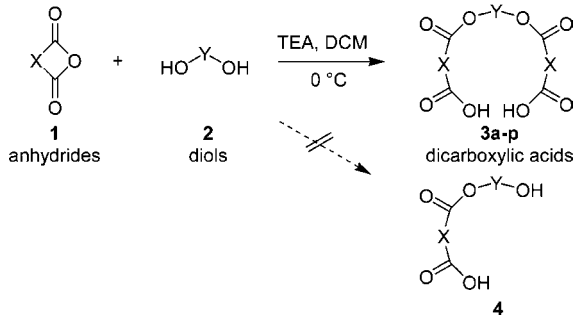
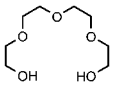
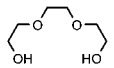
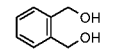
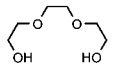
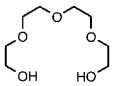
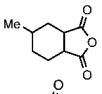
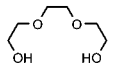
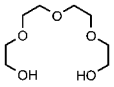
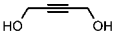
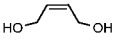
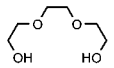
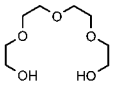
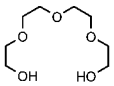
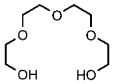


Table 1. Synthesis of Dicarboxylic Acids **3** via Scheme 1

entry	anhydride	diols	yields [a] (%)
a			90 (**3a**)
b			92 (**3b**)
c			88 (**3c**)
d			96 (**3d**)
e			94 (**3e**)
f			98 (**3f**)
g			96 (**3g**)
h			72 (**3h**)
i			92 (**3i**)
j			98 (**3j**)
k			94 (**3k**)
l			97 (**3l**)
m			99 (**3m**)
n			90 (**3n**)
o			88 (**3o**)
p			85 (**3p**)

[a] Yields are unoptimized and refer to isolated yields.

To extend this strategy, the reaction was performed with several cyclic anhydrides. Thus, the reaction was carried with the racemic anhydrides **1b**,**c**. The anhydride **1b** was reacted with *cis*-1,4-butenediol in the presence of triethylamine to

(12) (a) Bosch, M. P.; Guerrero, A. *Synlett* **2005**, *17*, 2611. (b) Zhi-Wei, G.; Sih, C. J. *J. Am. Chem. Soc.* **1988**, *110*, 1999.
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(14) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965.

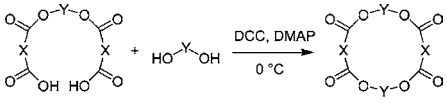
provide the corresponding dicarboxylic acid **3d** in an excellent yield. The anhydride **1b** was also reacted with tri(ethylene glycol) or tetra(ethylene glycol) to afford the dicarboxylic acids **3e**,**f** having oxyethylene moieties as spacers in very good yield. However, the reaction of unsymmetrical anhydride **1c** with tri(ethylene glycol) provided the dicarboxylic acid **3g** as a mixture of regioisomers. Similar reaction with anhydride **1d** with tetra(ethylene glycol) provided the dicarboxylic acid **3h**.

Next, we investigated the reactions involving *cis*-cyclic anhydrides **1e**−**g**. Initially, the reaction of 1,4-butynediol and an excess *cis*-cyclic anhydride **1e**, in the presence of triethylamine, afforded the corresponding dicarboxylic acid **3i**. Similar reactions were performed with the *cis*-anhydride **1e** and various diols such as *cis*-2-butene-1,4-diol, di(ethylene glycol), tri(ethylene glycol), and tetra(ethylene glycol) to afford the corresponding dicarboxylic acids **3j**−**m**.

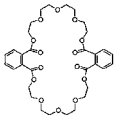
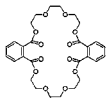
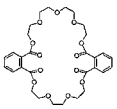
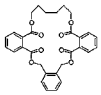
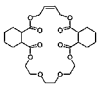
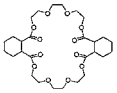
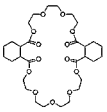
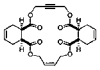
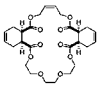
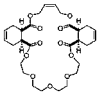
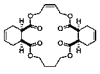
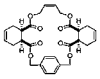
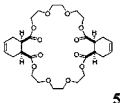
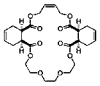
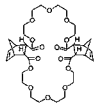
The desymmetrization of cyclic anhydride reactions was successfully carried out with *exo*- as well as *endo*-anhydrides. Thus, the *endo*-anhydride **1f** was reacted with tetra(ethylene glycol) to furnish the respective *endo*-dicarboxylic acid **3n**. Similarly, the reaction of *exo*-anhydride **1g** with di(ethylene glycol) or tetra(ethylene glycol) afforded the respective *exo*-dicarboxylic acids **3o**,**p**. All of the above reactions provided the corresponding dicarboxylic acids **3** in very good yields (Table 1) except the product **3h**. The NMR data characteristically evidenced a single isomer of the dicarboxylic acids **3** except in the case of **3g**. Formation of the corresponding hydroxy acids **4** was not observed in the above reactions as confirmed by spectroscopic data.

To synthesize the macrocyclic compounds, we planned to carry out the double esterification reaction of the above dicarboxylic acids **3**. To this end, the reaction of the dicarboxylic acid **3a**, tetra(ethylene glycol), and an excess DCC was carried out at 0 °C in the presence of a catalytic amount of DMAP to furnish the macrocyclic tetralactone **5a** in 61% yield (Table 2). The product **5a** was characterized on the basis of detailed spectroscopic studies. Interestingly, the linear dicarboxylic acid **3a** affords the macrocyclic tetralactone **5a** having 34 atoms in the cyclic core. To generalize the synthesis of macrocyclic tetralactones **5**, the representative dicarboxylic acids **3** were subjected to the double esterification reaction. To synthesize several tetralactones having different ring sizes, the double esterification reaction of dicarboxylic acid **3b** and tri(ethylene gycol) or tetra(ethylene glycol) was performed to afford the corresponding macrocyclic tetralactones **5b**,**c** in moderate yield. The products **5a**−**c** hold several oxyethylene units with 34, 28, and 31 atoms in the cyclic core, respectively (Table 2). Further, the reaction of dicarboxylic acid **3c** and 1,6-hexanediol provided the tetralactone **5d** having 22 atoms in the cyclic core. The dehydration reactions of dicarboxylic acids **3e**,**i**,**j**,**l**,**n** and *cis*-2-butene-1,4-diol, 1,4-butanediol, 1,4-benzenedimethanol, tri(ethylene glycol), or tetra(ethylene glycol) were carried out in the presence of DCC/DMAP to afford the corresponding macrocyclic tetralactones **5e**−**o** in moderate yield. Notably, this facile method affords many macrocyclic tetralactones **5** having 20, 22, 23, 24, 27, 28,

Table 2. Synthesis of Macrocyclic Tetralactones **5**



3 **2** **5**

entry	dicarboxylic acid	macrocyclic tetralactones	yields (%) [a]
a	**3a**	 **5a**	61
b	**3b**	 **5b**	54
c	**3b**	 **5c**	55
d	**3c**	 **5d**	61
e	**3e**	 **5e**	64
f	**3e**	 **5f**	68
g	**3e**	 **5g**	58
h	**3i**	 **5h**	60
i	**3j**	 **5i**	60
j	**3j**	 **5j**	65
k	**3j**	 **5k**	66
l	**3j**	 **5l**	58
m	**3l**	 **5m**	56
n	**3l**	 **5n**	72
o	**3n**	 **5o**	56

[a] Yields are unoptimized and refer to isolated pure compounds **5**.

31, and 34 atoms in the cyclic core. The cyclic anhydrides **1** except **1d** used in this experimental study provide macrocyclic tetralactones **5** having two fused cyclic/bicyclic ring systems on the macrocyclic core, which offer conformational rigidity to some extent. The structure of the tetralactone **5k** having fused *cis*-cyclohexene ring system was further confirmed using single-crystal X-ray crystallography (Figure 2).[15] The result of the high *R* value for the tetralactone **5k** is due to the extensive dynamic disorder[16] present in the aliphatic chain even at 100 K.

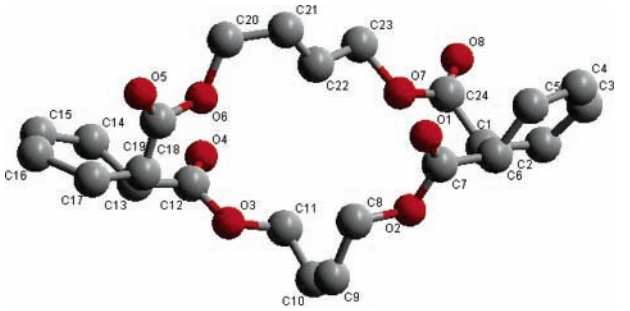
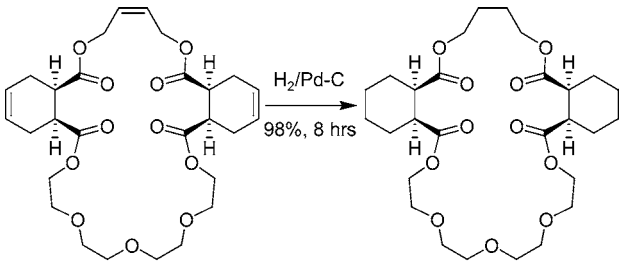


Figure 2. X-ray crystal structure of macrocyclic tetralactone **5k** (hydrogen atoms are omitted for clarity).

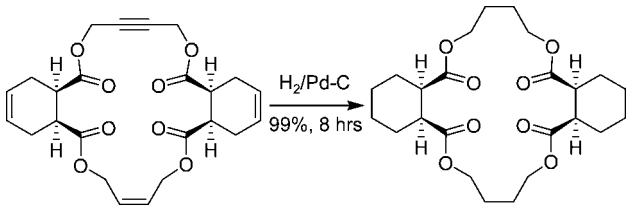
Finally, we were interested in reducing the double bonds of the unsaturated macrocyclic tetralactones in order to obtain a more flexible saturated macrocyclic core. Thus, the macrocyclic tetralactone **5j** was reduced by catalytic hydrogenation in the presence of 5 wt % of palladium on activated carbon to afford the saturated macrocyclic tetralactone **6** (Scheme 2). In this process, three double bonds are reduced under mild reaction conditions. This interesting multiple

Scheme 2



hydrogenation was also carried out with the tetralactone **5h** having the alkyne spacer to furnish the tetralactone **7** (Scheme 3). In this process, the triple bond is also reduced

Scheme 3



along with the double bonds. Thus, the unsaturated tetralactones having three double bonds and one triple bond are simultaneously reduced under mild reaction conditions.

In conclusion, we have developed a novel method to synthesize macrocyclic tetralactones in a facile manner from the commercially available materials. This methodology provides synthesis of medium as well as large interesting macrocyclic tetralactones having oxyethylene, alkenyl, alkynyl, alkyl, and aryl spacers in good yields. Further, the multiple reduction of unsaturated macrocyclic tetralactones was successfully performed to afford a fused saturated macrocyclic core under mild conditions. Work on the detailed application and chiral version of these crown ethers is under progress in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data for all new compounds, copies of spectra for the compounds **5b**−**e**,**h**,**j**−**m**, **6**, and **7**, and X-ray structural data for compound **5k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Crystal data for the compound **5k**: $C_{24}H_{19}O_8$, $M = 435.39$, $0.24 \times 0.13 \times 0.06$ mm^3, monoclinic, space group $P21/c$ with $a = 13.342(3)$ Å, $b = 9.981(3)$ Å, $c = 16.534(4)$ Å, $\alpha = 90°$, $\beta = 94.778(4)°$, $\gamma = 90°$, $V = 2194.2(10)$ Å^3, $T = 100(2)$ K, $R_1 = 0.1286$, $wR_2 = 0.3586$ on observed data, $z = 4$, $D_{calcd} = 1.318$ g cm^{-3}, $F(000) = 908$, absorption coefficient $= 0.100$ mm^{-1}, $\lambda = 0.71073$ Å, 7284 reflections were collected on a smart apex CCD single-crystal diffractometer, 2714 observed reflections ($I \geq 2\sigma(I)$). The largest difference peak and hole $= 0.714$ and -0.428 e Å^{-3}, respectively. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using SHELXL-97 software.

(16) The data collection was carried out at 100 K using liquid nitrogen and the extensive dynamic disorder observed in one of the bridging aliphatic chains with the cyclohexene rings during structure solution. Thus, carbon atoms C19, C20, C21, C22 and oxygen atoms O5, O6 of the chain are disordered along with one carbon atom C17 of the cyclohexene ring. The occupancy factors for these disordered atoms were fixed using FVAR from the SHELXTL (Sheldrick, G. M. SHELXTL, version 5.10, Bruker AXS, Madison, WI, 1997) program; all of the disordered atoms were refined only isotropically. Hydrogen atoms were fixed at geometrical positions for all of the non-hydrogen atoms refined anisotropically and not for the disordered atoms.