CHEMSUSCHEM

DOI: 10.1002/cssc.201000011

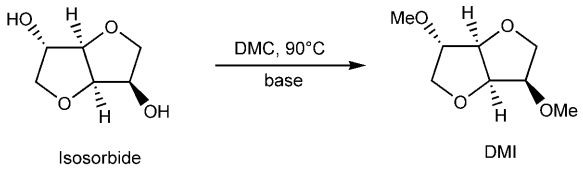
Green Synthesis of Dimethyl Isosorbide

Pietro Tundo,*[a, b] Fabio Aricò,[a, b] Guillaume Gauthier,[c] Laura Rossi,[d] Anthony E. Rosamilia,[a] Hanamanthsa S. Bevinakatti,[e] Robert L. Sievert,[e] and Christoper P. Newman[f]

In the last twenty years, new categories of solvents have been investigated in order to deal with safety and environmental issues;[1] that is, water,[2] supercritical fluids,[3] ionic liquids,[1a] solvents derived from CO_2[1b,4] or from renewables.[5] The advantage of using solvents derived from renewables is that natural products are present in large amounts, although only a small fraction (ca. 4%) is used for this purpose.

D-sorbitol is a good example of biofeedstock and has several applications in food and non-food industries. Besides, its cyclic derivate, isosorbide, is widely used in the pharmaceutical and hygiene industries. The methyl derivative of isosorbide, dimethyl isosorbide (DMI), is also extensively used in cosmetics and as a thinning agent.[6] Furthermore, due to its renewable starting materials and high boiling point (246 °C), DMI is also a suitable substitute of the more toxic currently used solvents, such as dimethylsulfoxide (DMSO), dimethylformamide (DMF), and dimethylacetamide (DMAc).[7] However, currently DMI is synthesized by common methylation reactions, which employ dimethyl sulfate (DMS) or methyl halides. Herein, it is reported an improved green synthesis of DMI by reaction of isosorbide with dimethyl carbonate (DMC) as reagent and solvent, in the presence of a base at reflux temperature of 90 °C. (Scheme 1).

DMC, nowadays produced by a clean and halogen-free process,[8] is an environmentally benign substitute of phosgene, DMS, and methyl halides and it is a well-known nontoxic solvent and reagent.[9,10] In general DMC, as a methylating agent (bimolecular, base-catalyzed, alkyl cleavage, nucleophilic substitution, $B_{Al}2$, mechanism)[4c] requires temperatures higher than 150 °C in the presence of a base. However, we previously reported that under similar conditions the reaction of hard alkoxides and DMC gave exclusively the transesterified methylcarbonates derivatives (via $B_{Ac}2$ mechanism), also at high temperatures.[11] On the contrary, other softer nucleophiles such as anilines, phenols and methylene-active compounds were easily methylated by DMC via a $B_{Al}2$ mechanism.[4,12] Methyl ethers of primary alcohols can be obtained through two steps: a $B_{Ac}2$ transesterification followed by the decarboxylation of the resulting methylcarbonate. However, methylation of secondary alcohols was never obtained quantitatively due to the formation of elimination products.[11] On the other hand, this is not the case in the present work; the secondary hydroxyls groups of isosorbide are efficiently methylated at reflux temperature (90 °C) by reaction with DMC in the presence of a range of bases (Table 1). This is quite surprising, especially in consideration of all the possible products that could be formed by reacting isosorbide with DMC, which include three classes of compounds (Figure 1): carboxymethyl derivates (MC-1, MC-2, dicarboxymethyl isosorbide (DC)), carboxymethyl methyl derivates (MCE-1, MCE-2), and methyl derivates (MMI-1, MMI-2 and DMI). In particular, it was possible to isolate all these isosorbide derivatives as pure compounds except MMI-2 and MC-2 due to their low amount in the reaction mixture. The isolated compounds were identified by GS–MS analysis and NMR spectroscopy (see the Experimental Section).



Scheme 1. Synthesis of dimethyl isosorbide.

Table 1 shows that the reaction of isosorbide with DMC in the presence of weak bases (entries 1–2), which led mostly to the formation of carboxymethylated products MC-1, MC-2, and DC.

However, reactions conducted in the presence of a strong base led to the formation of DMI with yields up to 40% (Table 1, entries 3–4). Increasing the amount of base (Table 1, entries 5–6), enhanced the yield of DMI. Quantitative conversion to DMI could be achieved using 3 equivalents of sodium methoxide. It is also interesting to point out that the methyl carboxymethyl derivative of isosorbide MCE-1 was formed in higher yields compared to MCE-2 (Table 1, entries 3–5). This result shows that the OH in *endo* position is more reactive towards methylation compared to the OH in *exo* position.

[a] *Prof. P. Tundo, Dr. F. Aricò, Dr. A. E. Rosamilia*
Consorzio Interuniversitario Nazionale "La Chimica per l'Ambiente"
(INCA - Interuniversity Consortium "Chemistry for the Environment")
Via delle Industrie 21/8 30175, Marghera Venice (Italy)
Fax:(+39) 0412346650
E-mail: tundop@unive.it

[b] *Prof. P. Tundo, Dr. F. Aricò*
Ca' Foscari Università di Venezia, Dipartimento Scienze Ambientali
Dorsoduro 2137-30123, Venice (Italy)

[c] *G. Gauthier*
École Nationale Supérieure de Chimie de Paris (ENSCP-Chimie ParisTech)
11 rue Pierre et Marie Curie, 75005 Paris (France)

[d] *Prof. L. Rossi*
Instituto de Investigaciones en Fisicoquímica de Córdoba (INFIQC)
Facultad de Ciencias Químicas, Departamento de Química Orgánica
Universidad Nacional de Córdoba, Ciudad Universitaria
CP 5000, Córdoba (Argentina)

[e] *Dr. H. S. Bevinakatti, R. L. Sievert*
Uniqema Ltd Wilton Centre, Room T425 Wilton, Redcar TS10 4R (United Kingdom)

[f] *C. P. Newman*
Quest International, Ashford, Kent TN24 0 LT (United Kingdom)

Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cssc.201000011.

Table 1. Reactions of isosorbide with DMC, Scheme 2, path a[a]

Entry	Base	Equivalents or w/w	Product distribution							
			Carbonates			Carbonate ethers		Ethers		
			MC-1	MC-2	DC	MCE-1	MCE-2	MMI-1	MMI-2	DMI
1	K_2CO_3	1.5	30 (23)[a]	7	59 (47)[b]	2	-	-	-	-
2	Cs_2CO_3	1 w/w	19	4	73 (65)[b]	3	1	-	-	-
3	NaOMe	1.5	-	1	6	30	12	11 (8)[b]	6	26 (20)[b]
4	*t*BuOK	1.5	-	-	-	37	18	2	2	40
5	NaOMe	2	1	1	11	36	8	1	1	41 (32)[b]
6	NaOMe	3	-	-	-	-	-	-	-	100 (98)[b]

[a] Isosorbide (2 g)/DMC (1:50); Reaction time: 20 h; Reaction conditions: 10^5 Pa, 90 °C. [b] Isolated yield.

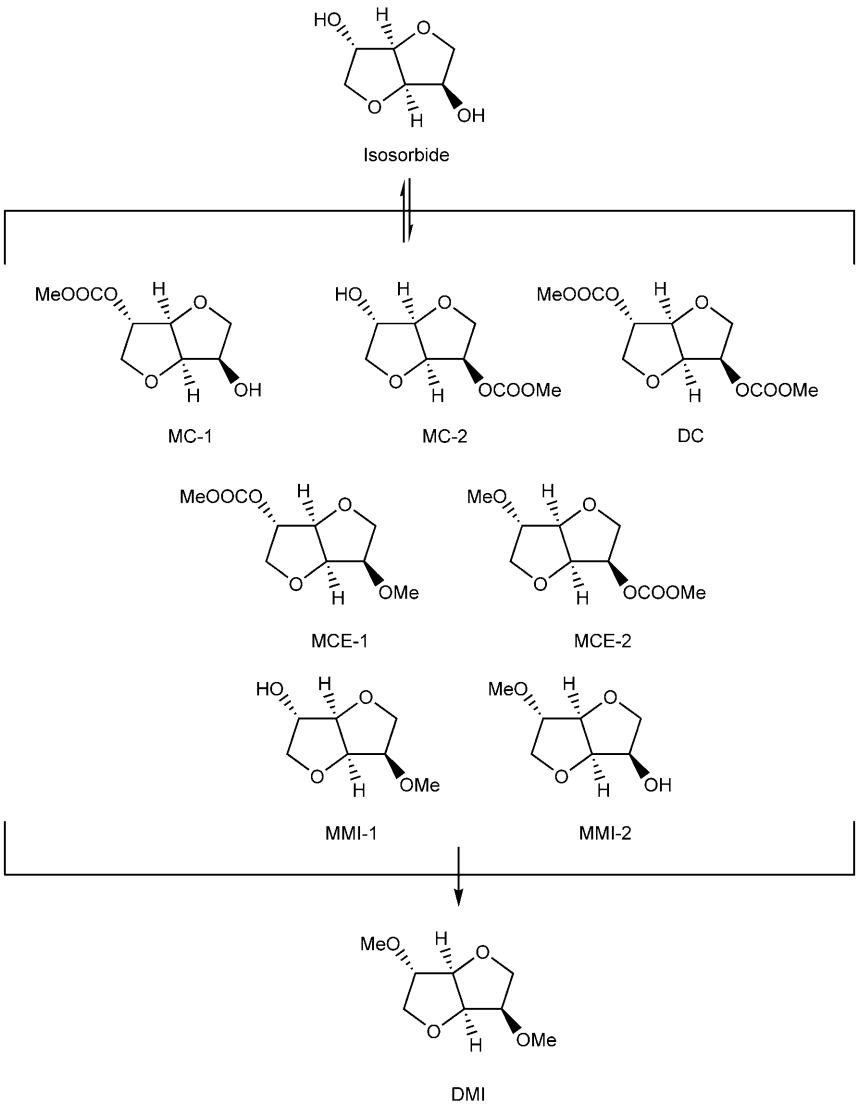
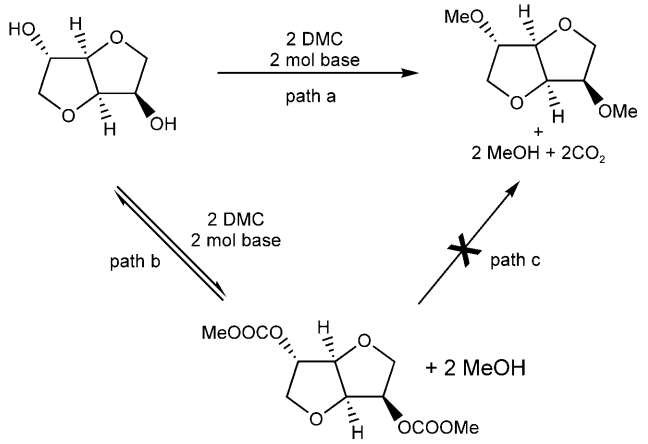


Figure 1. Carboxymethyl and methyl derivatives of isosorbide.

To gain some insights into the unusual reactivity of isosorbide, the dicarboxymethyl isosorbide (DC) was isolated as a pure compound and its involvement as intermediates in the synthesis of DMI was investigated. Thus, DC was reacted with NaOMe using either DMF or diglyme as solvents (see the Supporting Information). In both solvents, methylation of isosorbide did not occur. These results prove that the methylation reaction does not proceed via a decarboxylation reaction (Scheme 2, path c), but the mechanism operating in this case is $B_{Al}2$ substitution on the DMC molecule. Noteworthy, the pathways a, b, and c (methylation, carboxymethylation, and decarboxylation reactions) did not involve the chiral centers which remained unaffected during the reactions.

The remarkable reactivity of isosorbide towards methylation with DMC could be assigned to its unique structure. In fact, within isosorbide V-like configuration, each hydroxyl group is in the β-position to both furanic oxygens and this vicinity might enhance its reactivity towards DMC. Besides, the hydrogen of the *endo* hydroxyl group can form a strong intramolecular hydrogen bond (Figure 2a).[13] To understand the influence of the molecule backbone of secondary alcohols in a $B_{Al}2$ reaction, a number of substrates of similar structure were selected and their methylation was investigated. Table 2 shows the results obtained when the alcohols were reacted with an excess of NaOMe in refluxing DMC. Among the selected alcohols, isosorbide showed modified higher selectivity towards methylation. The other secondary alcohols formed methyl derivates in low to modest yields. In particular, 2-octanol gave only the carboxymethyl derivative whereas both propylene glycol propyl ether and 3-hydroxy-tetrahydrofuran methylated, but only in 9 and 14% yield, respectively.

To confirm this trend, a set of competition reactions was also performed using the same conditions (Table 3). In this case, isosorbide and the competing secondary alcohol were reacted in the same vessel in the presence of a base in DMC



Scheme 2. Possible reaction pathways for the methylation of isosorbide.

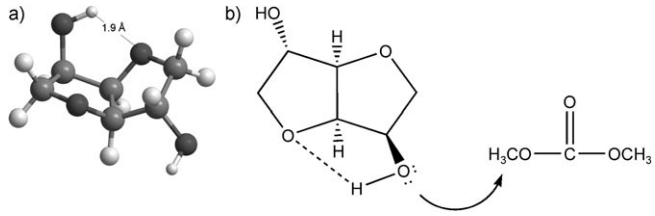
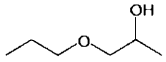
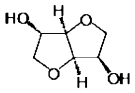


Figure 2. a) Isosorbide molecule. b) The reactivity of the *endo* hydroxyl group of isosorbide.

Table 2. Reactions of secondary alcohols with DMC and sodium methoxide at reflux conditions.[a]

Entry	Starting Reagent	Product Distribution		
		Conv.	Carbonate	Ether
1		100 (95)[b]	100 (95)[b]	-
2		100 (70)[b]	91 (68)[b]	9 (2)[b]
3		100 (86)[b]	86 (75)[b]	14 (11)[b]
4		100 (100)[b]	- (30)[b,c]	100 (40 DMI)[b,d]

[a] Alcohol/DMC (1:50); NaOMe (3 equiv.); Reaction time: 20 h; Reaction conditions: 10^5 Pa, 90 °C. [b] Product distribution after 8 h. [c] 30% of carbonates calculated as the sum of MCE-1 (23%); MCE-2 (7%). [d] Also obtained MMI-1 (18%); MMI-2 (10%).

under reflux (Table 3). The results collected confirmed the trend of reactivity towards methylation reported in Table 2. The selection of secondary alcohols mainly gave carboxymethyl derivates whereas isosorbide led to DMI as the major product.[14] The different reactivity among the investigated secondary alcohols is remarkable especially because the methylation of isosorbide involves two hydroxyl groups. This effect can be clearly ascribed to the rigidity of the structure that follows the trend: 2-octanol $\leq$ propylene glycol propyl ether $<$ 3-hydroxytetrahydrofuran $\ll$ isosorbide. Along this trend, the reaction pathway is modified (from $B_{Ac}2$ to a $B_{Al}2$) and the yield of the methylated product is enhanced.

The easy methylation of isosorbide could be attributed in a first instance to the acidity of the hydroxyl groups. However, the hydroxyl group in the *exo* position, which is more acidic than the *endo* hydroxyl group involved in a strong hydrogen bonding (Figure 2), showed to methylate at a slower rate as demonstrated by the lower yield of MCE-2 compared to MCE-1 (Table 1, entries 3–5).[15] Further investigations on the structure of isosorbide and on the effect of the hydrogen bonding are ongoing in order to understand its complex and unexpected reactivity.

In conclusion, the work herein is an example of efficient transformation of a renewable source into a product through free-halogen chemistry and opens up the way to further exploitation of DMI, as well as other carboxymethyl and methyl derivates of isosorbide. In general, halogen chemistry is characterized by an intensive use of energy and, in substitution reactions, by a fast reaction rate. To exploit chemistry without halogens and therefore to save energy,[16] we need to find alternative methods of molecular activation. These new reaction pathways should have low activation energy, being high yielding and as selective as in enzymatic reactions. From this point of view, the result on DMC and isosorbide reactivity is a step forward in this direction. Finally, this reaction is fascinating from a theoretical point of view for its complexity and also because it links nicely the idea of green chemistry with the exploitation of renewables resources.

Experimental Section

General information: ^{1}H NMR spectra were recorded at 300 MHz on a Bruker 300 Ultra Shield apparatus. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker apparatus 300 Ultra Shield. Chemical shifts are reported in ppm from the solvent resonance as an internal standard ($CDCl_3$). Analytical chromatography, TLC, was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on silica gel 60 Å grade 9385 (Merck 230–400 mesh). GC–MS analyses were performed on a Agilent 6890N gas chromatograph equipped with HP-5MS 30 m × 0.25 mm column and Agilent 5973 network mass selective detector. All the reactions were performed using dimethylcarbonate (Aldrich, 99% purity) dried on molecular sieves 4 Å.

Example of a reaction at reflux condition (Table 1): In a two-necked round bottom flask equipped with a dephlegmator, isosorbide (2.0 g, 0.014 mol, 1 equiv.), DMC (61.7 g, 0.658 mol, 50 equiv.), and sodium methoxide (2.2 g, 0.041 mol, 3 equiv.) were heated at reflux while stirring continuously under a nitrogen atmosphere. After 20 h, the reaction was stopped, the mixture was filtrated over Gooch n°4, and the DMC evaporated. The residual solution was distilled under vacuum to recover the crude reaction mixture. A sample was analyzed by GC–MS. The reaction mixture was subject-

Table 3. Competition reaction with selected secondary alcohols.[a]

Entry	Alcohols		Product distribution of isosorbide								Product distribution of alcohol		
	Isosorbide [equiv.]	Alcohol [equiv.]	Carbonates			Carbonate ethers		Ethers			ROH	$ROCO_2Me$	ROMe
			MC1	MC2	DC	MCE1	MCE2	MMI1	MMI2	DMI			
1	(1)	2-Octanol (1)	-	-	-	21	20	-	-	59	-	100	-
2	(1)	3-OH-tetrahydrofuran (1)	-	-	-	23	4	-	-	73	-	96	4
3	(1)	Propylene glycol propyl ether (1)	-	-	-	17	-	-	-	83	-	91	9

[a] Isosorbide (0.5 g)/DMC (1:50); NaOMe (6.0 equiv.); Reaction time: 20 h; Reaction conditions: 10^5 Pa, 90 °C.

ed to column chromatography. The gradient elution chromatography with DCM/MeOH (98:2) on silica gel allowed several of derivates to be isolated as pure compounds:

MC-2: $C_8H_{12}O_6$; M = 204.06 g mol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.12 (d, 1H), 4.64 (t, 1H), 4.52 (d, 1H), 4.31 (q, 1H), 4.12 (d, 1H), 3.99 (dd, 1H), 3.88 (dd, 1H), 3.80 (s, 3H,), 3.56 (dd, 1H), 2.59 ppm(d, 1H,); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 85.3, 81.9, 81.5, 73.5, 73.2, 72.2, 55.1 ppm.

DC: $C_{10}H_{14}O_8$; M = 262 g mol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.09 (d, 1H), 5.05 (t, 1H), 4.88 (t, 1H), 4.53 (d, 1H), 3.98–4.05 (m, 2H), 3.88–3.91 (m, 2H), 3.80 (s, 3H), 3.79 ppm(s, 3H,) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0, 154.6, 85.7, 81.0, 80.7, 76.5, 73.1, 70.3, 55.0, 54.9 ppm.

MCE-1: $C_9H_{14}O_6$; M = 218.08 g mol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.04 (t, 1H), 4.68 (t, 1H), 4.54 (d, 1H), 4.04 (d, 2H), 3.88–3.96 (m, 2H), 3.76 (s, 3H), 3.57–3.60 (m, 1H), 3.43 ppm (s, 3H,); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.7, 85.6, 81.6, 81.5, 80.4, 73.3, 69.9, 58.2, 54.9 ppm.

MCE-2: $C_9H_{14}O_6$; M = 218.08 g mol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.96 (t, 1H), 4.73 (t, 1H), 4.38 (d, 1H), 3.88–3.96 (d, 1H), 3.74–3.84 (m, 4H), 3.72 (s, 3H), 3.29 ppm (s, 3H,); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4, 85.6, 81.6, 81.5, 80.8, 73.1, 69.9, 58.2, 54.9 ppm.

MMI-1: $C_7H_{12}O_4$; M = 160.07 g mol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.71 (t, 1H), 4.43 (d, 1H), 4.29 (t, 1H), 3.86–3.98 (m, 4H), 3.55 (t, 1H), 3.45 (s, 3H), 2.56 ppm (s, OH,).

DMI: $C_8H_{14}O_4$; M = 174.09 g mol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.64 (t, 1H), 4.50 (d, 1H), 3.88–3.99 (m, 4H), 3.85 (m, 1H), 3.53–3.61 (m, 1H), 3.45 (s, 3H), 3.36 ppm (s, 3H). All spectroscopic features of this product correspond to those reported in the literature.

Example of a reaction with DMC at reflux condition (Table 2): In a two-necked round bottom flask equipped with a dephlegmator, 3-hydroxy-tetrahydrofuran (2.0 g, 0.022 mol, 1 mol. equiv), DMC 102 g (1.13 mol, 50 mol. equiv), and sodium methoxide (7.3 g, 0.136 mol, 3 equiv.) were heated at reflux while stirring continuously under a nitrogen atmosphere. After 20 h the reaction was stopped, the mixture was filtrated over Gooch n°4, and the DMC evaporated. The residual solution was distilled under vacuum to recover the crude reaction mixture that was then analyzed by GC–MS.

Example of a reaction with DMC at reflux condition (Table 3): In a two-necked round bottom flask equipped with a dephlegmator, isosorbide (0.5 g, 0.0034 mol, 1 equiv.), DMC (16 g, 0.171 mol, 50 equiv.), 3-hydroxy-tetrahydrofuran (0.3 g, 0.0034 mol, 1 equiv.), and sodium methoxide (2.2 g, 1.1 mol, 3 equiv.) were heated at reflux while stirring continuously under a nitrogen atmosphere. After 20 h the reaction was stopped, the mixture was filtrated over Gooch n°4, and the DMC evaporated. The residual solution was distilled under vacuum to recover the crude reaction mixture that was then analyzed by GC–MS.

Acknowledgements

We want to acknowledge the Imperial Chemical Industries Ldt (ICI) for the support and funding.

Keywords: carbohydrates · carbonates · green chemistry · methylation · renewable resources

[1] a) P. Tundo, A. Perosa, F. Zecchini, *Methods and Reagents for Green Chemistry*, John Wiley and Sons, NJ, **2007**; b) P. Tundo, V. Esposito, *Green Chemistry Reactions*, Springer, Dordrecht, **2008**; c) W. Leitner, *Green Chem.* **2009**, *11*, 603.

[2] a) J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *435*, 746–747; b) S. Narayan, J. Muldoon, M. G. Finn, *Angew. Chem.* **2005**, *117*, 3339–3343; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279.

[3] M. Poliakoff, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas, *Science* **2002**, *297*, 807–810.

[4] a) M. Selva, A. Bomben, P. Tundo, *J. Chem. Soc. Perkin Trans. 1* **1997**, *7*, 1041; b) A. Bomben, M. Selva, P. Tundo, *Ind. Eng. Chem. Res.* **1999**, *38*, 2075; c) P. Tundo, M. Selva, A. Perosa, S. Memoli, *J. Org. Chem.* **2002**, *67*, 1071; d) P. Tundo, L. Rossi, A. Loris, *J. Org. Chem.* **2005**, *70*, 2219–2224; e) A. E. Rosamilia, F. Aricò, P. Tundo, *J. Org. Chem.* **2008**, *73*, 1559–1562.

[5] B. Oster, W. Fechtel in *Ullmann's Encyclopedia Industrial Chem.* **1994**, *A25*, 418–423.

[6] P. Tundo, M. Selva, *Acc. Chem. Res.* **2002**, *35*, 706.

[7] a) O. Dudeck, O. Jordan, K. T. Hoffmann, A. F. Okuducu, K. Tesmer, T. Kreuzer-Nagy, D. A. Rü fenacht, E. Doelker, R. Felix, *AJNR Am. J. Neuroradiol.* **2006**, 27, 1900–1906; b) M. Sawyer, A. E. Ekpe; M. W. Wu, US 6383515, **1999**; c) A. East, M. Jaffe, Y. Zhang, L. H. Catalani, US 20080021209, **2008**.

[8] The Merck Index, 11th Ed., S Budavari, NJ, USA, **1989**.

[9] a) A. Otto, J. W. Wiechers, C. L. Kelly, J. Hadgraft, J. Du Plessis, *Skin Pharmacol. Physiol.* **2008**, *21*, 326–334; b) E. Squillante, T. Needham, A. Maniar, S. Kislalioglu, H. Zia, *Eur. J. Pharm. Biopharm.* **1998**, *46*, 265–271.

[10] a) U. Romano, F. Rivetti, N. Di Muzio, US Patent 4318862, **1979**; b) F. Rivetti, P. Tundo, P. Anastas, *Green Chemistry: Challenging Perspectives*, Oxford University Press: Oxford, **2000**, p 201; c) D. Delledonne, F. Rivetti, U. Romano, *J. Organomet. Chem.* **1995**, *488*, C15–C19.

[11] P. Tundo, S. Memoli, D. Hérault, K. Hill, *Green Chem.* **2004**, *6*, 609–612.

[12] a) P. Tundo, G. Moraglio, F. Trotta, *Ind. Eng. Chem. Res.* **1989**, *28*, 881; b) A. Bomben, C. A. Marques, M. Selva, P. Tundo, *Tetrahedron* **1995**, *51*, 11573; c) A. Bomben, M. Selva, P. Tundo, *J. Chem. Res.* **1997**, 448; d) S. Memoli, M. Selva, P. Tundo, *Chemosphere* **2001**, *43*, 115.

[13] a) F. J. Hopton, G. H. S. Thomas, *Can. J. Chem.* **1969**, *47*, 2395; b) Y. Zhu, M. Durand, V. Molinier, J. M. Aubry, *Green Chem.* **2008**, *10*, 532–540.

[14] The yield of DMI in this case is not quantitative due to the lower amount of base used (ca. 30% equivalents less compared to Tables 1 and 2)

[15] In this case study, the OH group labeled as *endo* refers to the OH pointing toward the isosorbide V-shaped cavity, whereas the *exo* OH group refers to the OH pointing out of the V-shaped cavity of isosorbide.
[16] European production of chlorine is 20 million tonnes per year in 80 plants which in turn generates 5.21 trillion tonnes of CO_2 equivalents per year with a primary energy consumption of 55 trillion GJ per year; in Europe, chlorine use accounts for 0.45% of the global warming potential.

Received: January 19, 2010
Revised: February 17, 2010
Published online on April 16, 2010

