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Natural Product Research
Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: http://www.tandfonline.com/loi/gnpl20

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To cite this article: Jesus M. Rodilla, Patricia P. Neves, Sofia Pombal, Vicente Rives, Raquel Trujillano & David Díez (2015): Hydrotalcite catalysis for the synthesis of new chiral building blocks, Natural Product Research, DOI: 10.1080/14786419.2015.1075525

To link to this article: http://dx.doi.org/10.1080/14786419.2015.1075525

NATURAL PRODUCT RESEARCH, 2015
http://dx.doi.org/10.1080/14786419.2015.1075525

Hydrotalcite catalysis for the synthesis of new chiral building blocks

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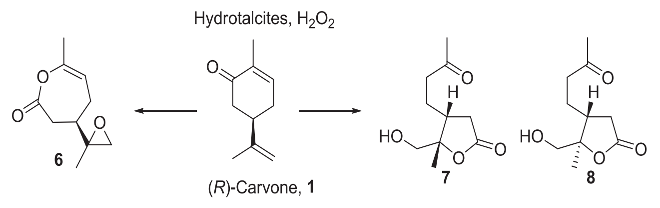
ABSTRACT
The use of hydrotalcites for the synthesis of two chiral building blocks in a simple way is described as a new and green methodology. The synthesis of these compounds implies a regioselective Baeyer–Villiger reaction in a very selective way with ulterior opening and lactonisation. This methodology should be considered green for the use of hydrogen peroxide as the only oxidant and hydrotalcites as the catalyst, and because no residues are produced apart from water. The procedure is very adequate for using in gram scale, in order to increase the value of the obtained compounds. The conditions are excellent and can be applied for nonstable compounds, as they are very mild. The synthesised compounds are magnific starting materials for the synthesis of biologically active or natural compounds. The use of a cheap, commercial and chiral compound as carvone disposable in both enantiomeric forms adds an extra value to this methodology.



ARTICLE HISTORY
Received 13 May 2015
Accepted 14 July 2015

KEYWORDS
Hydrotalcites; natural products; terpenes; hydrogen peroxide; carvone

1. Introduction

Carvone **1** is a versatile starting material for the syntheses of biological active natural products and disposable in both enantiomeric forms, terpenes being the main objective from this natural product (Macaev 2013). One of the more important derivatisations of carvone structure is the epoxidation. This reaction can be done in a regioselective way with epoxidation of the exocyclic to give **2** or endocyclic double bond to give **3**, based on electron-rich

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The supplementary material for this paper is available online at http://dx.doi.org/10.1080/14786419.2015.1075525.

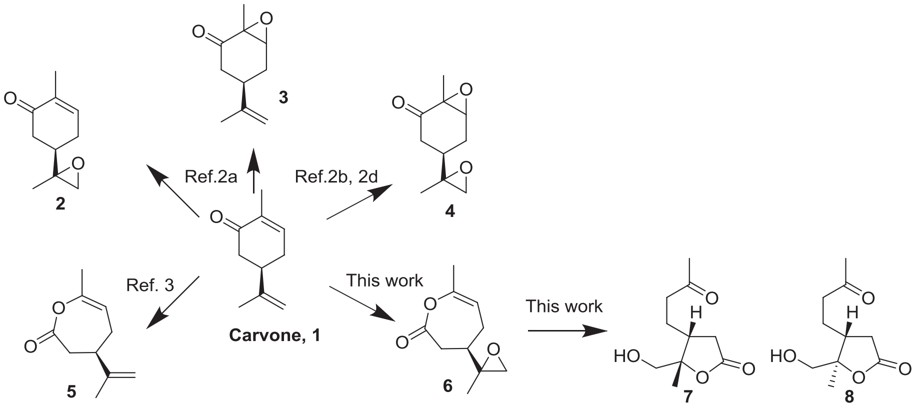


Figure 1. Epoxidation and Baeyer–Villiger products obtained from (*R*)-carvone.

or electron-deficient epoxidation (Murphy et al. 2003; Mak et al. 2006; Uguina, Delgado, Carretero 2009; Uguina, Delgado, Carretero, Gomez-Diaz 2009). By contrary, diastereoselectivity in this class of epoxidations is not good (Figure 1).

Due to the importance of carvone as starting material, there has been much interest too in the synthesis of compound **5** by a Baeyer–Villiger type reaction (Frisone et al. 1993; Lei et al. 2007). This compound has been obtained from carvone by heterogeneous Baeyer–Villiger oxidation with H_2O_2/acetonitrile using Mg/Al hydrotalcite (Llamas et al. 2007) or by transition metals complexes as catalysts (Brunetta & Strukul 2004). These reactions were followed by GLC or by GC–MS analysis, so in order to obtain compounds as building blocks, it is necessary to isolate and determine them properly. The interest was to obtain a compound as **6**, using friendly reagents as oxygen peroxide and hydrotalcite as catalyst (Figure 1).

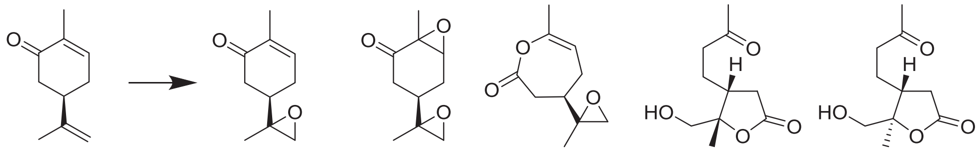
Layered double hydroxides, also known as hydrotalcite-like compounds, are layered compounds characterised by their interlayer space, chemical composition and sequence of layer stacking (Bookin & Drits 2001). Their general formula is $[M^{2+}{}_{1-x}M^{3+}{}_{x}(OH)_2]^{x+}[A^{n-}]_{x/n}\cdot mH_2O$, where M^{2+} and M^{3+} are the di- and trivalent metal cations, respectively, and A^{n-} is the interlayer anion (Rives 2001). Its structure is similar to that of brucite, $Mg(OH)_2$, where each Mg^{2+} ion is octahedrally coordinated by six hydroxyl groups and the octahedra share edges forming infinite layers. These layers are stacked and bonded through hydrogen bond and contain water molecules between the layers. If some Mg^{2+} ions are isomorphically replaced by cations with a higher oxidation state, but similar radii, the brucite layers will become positively charged; the electrical balance is achieved by means of anions located in the interlayer space, together with water molecules. The easiness of their synthesis and the possibility of changing their chemical composition in a wide range make this layered solids and their derivatives very interesting as catalysts in different reactions. Their performance as catalysts in different catalytic reactions has been studied by changing their composition, molar ratio, synthesis method, etc. (Cavani et al. 1991; Rives et al. 1998; Monzón et al. 1999; Jiménez-Sanchidrián & Ruiz 2008; Rives et al. 2010).

2. Results and discussion

In order to have the required compounds, we start the study with a Lewis acid as $AlCl_3$ using as oxidant hydrogen peroxide. In these conditions, entries 1 and 2 were observed that the epoxidation only took place in the terminal double bond to give epoxide **2** and moderate yield of the desired compounds **7** and **8**. The absolute stereochemistry was determined by NOESY as one of the chiral centres is known in the starting material. As can be understood, these compounds are the result of terminal double bond epoxidation of carvone, Baeyer–Villiger oxidation of the ketone and opening of the epoxide by the acid group resulting of the lactone in compound **6**. With these compounds in hand, it was decided to proceed to obtain them not only in better yield but in more green procedure. For this reason, we decide to use hydrotalcite in order to obtain these useful compounds. When the reaction was done with hydrotalcite obtained as described before, using SDS and hydrogen peroxide as oxidant, the synthesis of compounds **7** and **8** was achieved in good yield entry 7 (Table 1), as it recovered an important quantity of the starting material, and complete recovering of the catalyst was achieved. It should be underlined that when using Mg_4/Al-CO_3 hydrotalcite as catalyst instead of $AlCl_3$, there is an important change in the nature of the catalyst as hydrotalcite has a strongly basic character. The catalyst was prepared by simple coprecipitation from Mg and Al nitrates at constant pH. SDS does not enter in the interlayer space, as there is a strong affinity of hydrotalcite for carbonate; moreover, such an affinity is larger for divalent (carbonate) than for monovalent (SDS) anions, so the catalyst active form is Mg_4/Al-CO_3. It has to be signalled that compound **2** is an intermediate to the final compounds **7** and **8**. It was tried to the use of *m*-CPBA as oxidant and hydrotalcite as catalyst. In this case, we were able to obtain compound **6** although in low yield.

As we have said before, compound **2** is the intermediate for the target molecules **7** and **8**. So as it is a compound already known and easy to obtain, it was decided to use it as starting material and to test our conditions with this compound, using the same methodology, table 2. When used in conditions with AlCl3 and hydrogen peroxide as oxidant, entries 1 and 2, it was achieved only the desired compounds 7 and 8 in low yield and other compounds as the diol 9 and epoxide 10 resulting of the opening of the epoxide of 2 and epoxidation of the enol intermediate, respectively. Again the use of hydrotalcite increases considerably the yield of

Table 1. Screening of catalysts and conditions for the Baeyer–Villiger reaction of (R)-carvone.



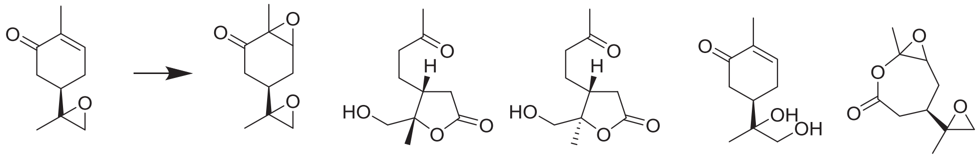
Carvone, 1 **2** **4** **6** **7** **8**

Entry	Conditions	Temperature	Time	Yield[a](%)					
				1	**2**	**4**	**6**	**7**	**8**
1	A	75	48 h	40.0	28.0	–	–	10.0	6.0
2	A	75	160 h	39.0	25.0	–	–	15.0	12.0
3	B	50	96 h	50.0	18.0	2.0	–	6.0	5.0
4	B	40	200 h	10.0	31.0	10.0	–	25.0	19.5
5	B	40	300 h	8.0	45.0	20.0	–	9.2	8.4
6	B	40	400 h	5.0	60.0	30.0	–	6.0	5.3
7	B	60	100 h	14.0	25.0	12.0	–	27.0	26.0
8	C	40	5 h	–	70.0	4.0	12.0	–	–

Conditions: A. EtOH (25 mL), $AlCl_3$ (65 mg), H_2O_2 30% (0.80 mL); B. Benzonitrile (1.50 mL), H_2O_2 30% (1.30 mL), Hydrotalcite (29 mg), SDS (sodium dodecyl sulphate) (73 mg), EtOH (1.50 mL); C. Hydrotalcite (39 mg), *m*-CPBA (metachloroperbenzoic acid) (782 mg), CH_2Cl_2 (15 mL).

[a]The yield until 100% are decomposition or undetermined products.

Table 2. Screening of Baeyer–Villiger reaction of the epoxy-carvone.



2 **4** **7** **8** **9** **10**

Entry	Conditions	Temperature	Time	Yield[a](%)					
				2	**4**	**7**	**8**	**9**	**10**
1	A	40	24 h	30.0	–	11.0	10.0	8.2	–
2	A	40	30 h	33.0	–	14.0	12.0	10.5	–
3	A	70	72 h	34.1	–	18.0	15.0	17.2	–
4	B	65	24 h	34.1	17.2	19.0	18.1	–	–
5	B	75	384 h	33.0	10.0	12.0	11.0	–	–
6	B	60	168 h	26.0	9.0	27.0	25.0	–	–
7	C	40	28 h	–	20.0	21.0	19.0	–	15.2

Conditions: A. EtOH (25 mL), $AlCl_3$ (65 mg), H_2O_2 30% (0.80 mL); B. Benzonitrile (1.50 mL), H_2O_2 30% (1.30 mL), Hydrotalcite (29 mg), SDS (73 mg), EtOH (1.50 mL); C. Hydrotalcite (39 mg), *m*-CPBA (metachloroperbenzoic acid) (782 mg), CH_2Cl_2 (15 mL).

[a]The yield until 100% are decomposition or undetermined products.

the desired compounds **7** and **8**, taking in account the amount of recovered starting material (Table 2). The use of *m*-CPBA as oxidant not increases the yield in the required compounds.

3. Experimental

3.1. General procedure for the reaction with $AlCl_3$

In a round-bottom flask equipped with a reflux condenser, carvone **1** (300 mg, 2 mmol), $AlCl_3$ (60 mg, 0.45 mmol), H_2O_2 30% (0.12 mL, ~2 eq) and 50 mL of EtOH were heated at 75 ºC while stirring. The progress of the reaction was monitored TLC. After 48 h, the reaction was extracted with DCM, washed with water, dried and the solvent evaporated. Finally, the pure compound was obtained by flash chromatography on silica gel (hexane/EtOAc 8 : 2) to obtain **1** (39.0%), **2** (25.0%), **7** (15.0%) and **8** (12.0%).

(4R,5S)-5-(hydroxymethyl)-5-methyl-4-(3-oxobutyl)dihydrofuran-2(3H)-one 7

Compound **7** was purified by flash chromatography (silica gel, hexane/EtOAc 6 : 4). IR (film): 3419, 2976, 2937, 1746, 1709, 1663, 1382, 1220, 1058, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (1H, d, *J* 12.4 Hz, H-1″a), 3.64 (1H, d, *J* 12.4, H-1″b), 2.50 (2H, m, H-3), 2.40 (2H, m, H-2′), 2.21 (1H, m, H-4), 2.14 (3H, s, Me-4′), 1.83 (2H, m, H-1′), 1.29 (3H, s, Me-1‴); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1 C-3′; 177.2 C-2; 36.0 C-3, 44.6 C-4; 22.7 C-1′; 42.1 C-2′; 30.0 C-4′, 88.4 C-5; 66.0 C-1″; 22.4 C-1‴; HRMS (EI) calcd for $C_{10}H_{16}O_4Na$ requires (M + Na) 223.0940; found 223.0934.

(4R,5S)-5-(hydroxymethyl)-5-methyl-4-(3-oxobutyl)dihydrofuran-2(3H)-one 8

Compound **8** was purified by flash chromatography (silica gel, hexane/EtOAc 6 : 4). $[\alpha]_D^{20}$ = −14.7 (*c* = 0.4, $CHCl_3$); IR (film): 3420, 2977, 2931, 1744, 1708, 1662, 1418, 1367, 1219, 1059, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (1H, d, *J* 12.4 Hz, H-1″a), 3.54 (1H, d, *J* 12.4 Hz, H-1″b), 2.58 (1H, m, H-4), 2.49 (2H, m, H-3′), 2.33 (1H, d, *J* 10.5 Hz, H-3a), 2.29 (1H, d, *J* 10.5 Hz, H-3b), 2.17 (3H, s, Me-4′), 1.78 (1H, m, H-1′a), 1.57 (1H, m, H-1′b), 1.26 (3H, s, Me-1‴); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5 C-3′; 175.2 C-2; 34.8 C-3; 38.2 C-4; 23.4 C-1′; 41.9 C-2′; 30.3 C-4′, 88.6 C-5; 66.8 C-1″; 17.6 C-1‴; HRMS (EI) calcd for $C_{10}H_{16}O_4Na$ requires $(M + Na)^+$ 223.0940; found 223.0934.

The reaction was also performed from compound **2**, under the same conditions. By the flash CC in the same conditions, we have obtained the following compounds: **2** (34.1%), **7** (18.0%), **8** (15.0%) and **9** (17.2%).

8,9-dihydroxycarvone, 9

Compound **9** was purified by flash chromatography (silica gel, hexane/EtOAc 7 : 3) as a mixture of isomers. IR (film): 3436, 2975, 2924, 1655, 1432, 1370, 1104, 1056, 745 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (1H, m, H-6), 3.56 (2H, m, H-9), 2.80–2.20 (5H, m, H-3, 4 and 5), 1.78 (3H, s, Me-7) and 1.26 (3H, s, Me-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5 C-1; 199.2 C-2; 38.6 C-3; 41.8 C-4; 26.4 C-5; 144.1 C-6; 15.8 C-7; 72.8 C-8; 57.8 C-9; 21.9 C-10; HRMS (EI) calcd for $C_{22}H_{25}O_5Na$ requires (M + Na) 438.1345; found 438.1349.

3.2. General procedure for the reaction with hydrotalcite and H_2O_2

In a round-bottom flask equipped with a reflux condenser, Carvone **1** (300 mg, 2 mmol), benzonitrile (0.82 mL, 8 mmol), H_2O_2 30% (0.12 mL, 4 mmol), hydrotalcite $Mg_4/Al–CO_3$ (17.0 mg), SDS (35 mg, 0.10 mmol) and EtOH (0.87 mL) were heated at 40–60 °C while stirring. The progress of the reaction was monitored by TLC. After 50–250 h, the reaction was extracted with DCM, washed with water, dried and the solvent evaporated. Finally, the pure compound was obtained by flash column chromatography on silica gel, **1** (15.0%), **2** (25.0%), **4** (12.0%) **7** (27.0%) and **8** (26.0%).

The reaction was also performed with compound **2**, as starting material under the same conditions. By flash CC (in the same conditions), the following compounds were obtained: **2** (26.0%), **4** (9.0%), **7** (27.0%) and **8** (25.0%).

3.3. General procedure for the reaction with hydrotalcite and m-CPBA

In a round-bottom flask equipped with a reflux condenser, carvone **1** (505 mg, 3.4 mmol), hydrotalcite (39.0 mg), MCPBA (782 mg, 4.5 mmol) and DCM (15.0 mL) were heated at 40 ºC while stirring. The progress of the reaction was monitored by TLC. After 5 h, the reaction was extracted with DCM, washed with water, dried and the solvent evaporated. Finally, the pure compound was obtained by flash column chromatography on silica gel, **2** (70.0%), **4** (4.0%) and **6** (12.0%).

8,9-epoxicarvone-1,2-olide 6

Compound **6** was purified by flash chromatography (silica gel, hexane/EtOAc 8 : 2) as a mixture of isomers. IR (film): 2973, 2930, 1715, 1660, 1381, 1223, 1058, 950 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, td, J_1 7.3 Hz and J_2 1.2 Hz, H-6), 2.68 (2H, dd, J_1 7.0 Hz and J_2 1.4 Hz, H-3), 2.64 (1H, dd, J_1 4.0 Hz and J_2 0.9 Hz, H-9a), 2.57 (1H, d, J 4.5 Hz, H-9b), 2.31 (1H, t, J 7.1 Hz, H-4), 2.20–2.10 (2H, m, H-5), 1.89 (3H, s, Me-7), 1.34 (3H, s, Me-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2 C-1; 171.0 C-2; 34.7 C-3; 46.1 C-4; 23.8 C-5; 107.8 C-6; 19.3 C-7; 58.2 C-8, 52.9 C-9, 18.5 C-10; HRMS (EI) calcd for $C_{10}H_{14}O_3Na$ requires $(M + Na)^+$ 205.0835; found 205.0832.

The reaction was also performed with compound **2**, as starting material under the same conditions. By flash CC (in the same conditions), we have obtained the following compounds: **4** (20.0%), **7** (21.0%), **8** (19.0%) and **10** (15.2%).

1,6;8,9-Diepoxycarvone-1,2-olide 10

Compound **10** was purified by flash chromatography (silica gel, hexane/EtOAc 8 : 2) as a mixture of isomers. IR (film): 2974, 2927, 1720, 1418, 1380, 1229, 1100, 1069, 958, 750 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.15 (1H, dd, J_1 8.6 Hz and J_2 5.3 Hz, H-6), 2.83 (2H, dd, J_1 8.4 Hz and J_2 2.1 Hz, H-3), 2.66 (1H, dd, J_1 4.5 Hz and J_2 0.9 Hz, H-9a), 2.62 (1H, d, J 4.5 Hz, H-9b), 2.45 (1H, dt, J_1 13.9 Hz and J_2 5.3 Hz, H-5a), 2.03 (1H, dddd, J_1 13.9 Hz, J_2 8.4 Hz, J_3 5.3 Hz and J_4 2.1 Hz, H-4), 1.71 (3H, s, Me-7), 1.38 (1H, dt, J_1 13.9 Hz and J_2 8.6 Hz, H-5b), 1.33 (3H, s, Me-10);^{13}C NMR (100 MHz, CDCl$_3$) δ 168.5 (C-2); 83.2 (C-1); 58.9 (C-6); 58.6 (C-8); 53.5 (C-9); 37.6 (C-4); 34.8 (C-3); 29.1 (C-5); 20.4 (C-7); 18.0 (C-10); HRMS (EI) calcd for $C_{25}H_{32}O_5$ $(M + H)^+$, 458.1995; found 458.1978.

4. Conclusions

It has been demonstrated that the use of hydrotalcites made possible to obtain in good yield from a commercially available material in both enantiomeric pure forms chiral compounds such as lactones **7** and **8** that can be used in organic synthesis as valuable synthons (Valeev et al. 2010).

Acknowledgements

C. Raposo is acknowledged for the Mass Spectra and Chemical Analyses.

Funding

JMR, PPN, SF and DD thank the F.S.E. and Junta de Castilla y León [GR178], and VR and RT thank Ministerio de Ciencia e Innovación [grant number MAT2009-08526] for the financial support.

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