



Acylation

Efficient O-Acylation of Alcohols and Phenol Using Cp₂TiCl as a **Reaction Promoter**

María Jesús Durán-Peña,^[a] José Manuel Botubol-Ares,^[a] James R. Hanson,^[b] Rosario Hernández-Galán,^[a] and Isidro G. Collado*^[a]

Abstract: A method has been developed for the conversion of primary, secondary, and tertiary alcohols, and phenol, into the corresponding esters at room temperature. The method uses a titanium(III) species generated from a substoichiometric amount of titanocene dichloride together with manganese(0)

as a reductant, as well as methylene diiodide. It involves a transesterification from an ethyl ester, or a reaction with an acyl chloride. A radical mechanism is proposed for these transformations.

Introduction

Transesterification and acylation reactions are important transformations in organic chemistry, and esters are widely found in many naturally occurring compounds.^[1] Although a number of methods have been reported for the acylation of alcohols, some of these use bases, elevated temperatures, or lengthy workup procedures. In some instances, the methods are incompatible with particular functional groups.^[2]

We have recently developed new methods for the cyclopropanation of allylic alcohols^[3] and for the tetrahydrofuranylation and tetrahydropyranylation of alcohols,[4] catalysed by low-valent titanium species. We obtained either the cyclopropanated product or the THF/THP ether, depending on the alkyl halide used. Furthermore, we observed that when the cyclopropanation reaction of geraniol mediated by a Ti^{III} species was quenched by the addition of ethyl acetate, transesterification occurred, giving the acetates of geraniol (3b) and its cyclopropyl derivative $[(\pm)-3a]$ rather than compounds $[e.g., (\pm)-2]$ retaining the free hydroxy group. This result shows that activated species derived from geraniol and cyclopropylgeraniol were present in the solution. This unexpected observation has led to a mild and efficient method for the esterification of a wide variety of primary and secondary alcohols mediated by a Ti^{III} species. In this paper, we report our recent results on the first transesterification and O-acylation of alcohols mediated by Cp₂TiCl in the presence of CH₂l₂ and an ester or an acyl chloride. This method gives esters from primary, secondary, and ter-

[a] Departamento de Química Orgánica, University of Cádiz, Facultad de Ciencias. Polígono Río San Pedro s/n, 11510 Puerto Real, Cádiz, Spain E-mail: isidro.gonzalez@uca.es http://www.isidrogcollado.es/

[b] Department of Organic Chemistry, University of Sussex, Brighton, Sussex, BN1 9QJ, United Kingdom

Supporting information and ORCID(s) from the author(s) for this article are Ð

available on the WWW under http://dx.doi.org/10.1002/ejoc.201600496.

tiary alcohols, and from phenol, under mild conditions at room temperature.

Results and Discussion

 $Bis(cyclopentadienyl) titanium(III) \ chloride, \ Cp_2 Ti^{III} CI, {}^{[5]} \ has \ be$ come a very popular reagent in radical reactions because of its soft one-electron-reductive character.^[6] This complex is tolerated by a variety of functional groups.^[7] In our previous work, we prepared Cp₂Ti^{III}CI in situ by stirring a red solution of commercially available Cp₂TiCl₂ (0.5 equiv.) with manganese dust (12.8 equiv.) in dry and degassed tetrahydrofuran to give a green solution of the Ti^{III} complex.^[8] A solution of the allylic alcohol geraniol (1; 1 equiv.) together with CH₂I₂ (5 equiv.) was then added, and the mixture was stirred for 2.5 h. The reaction was guenched under an inert gas with ethyl acetate (2 equiv.) to give acetates (\pm) -**3a** and **3b** guantitatively (Scheme 1).^[3]



Scheme 1. Preparation of compounds (\pm) -2, (\pm) -3a, and 3b.

As part of our work on exploring the reactivity of Ti^{III} species and developing new titanium-catalysed reactions, we examined the role of each reagent and the scope of the esterification reaction. We evaluated the roles of titanium, manganese, and diiodomethane in the reaction (see Table 1). We observed that the transesterification did not proceed in the absence of CH₂I₂ (Entry 2, Table 1). Furthermore, the initial generation of a Ti^{III} species from Ti^{IV} and Mn⁰ was required. No reaction was observed in the absence of either Ti^{IV} or manganese dust, indicat-





ing that both titanium and manganese participated in the reaction (Entries 3–6, Table 1).

Table 1. Acetylation of geraniol (1) using different reaction conditions under base-free conditions.

		(1) Cp₂TiCl₂, Mn, CH₂l₂, THF, r.t., 2.5 h		
HO	geraniol (1)	(2) AcOl r.t., 1.5 I	Et (2 equiv.), n	3b
Entry	Ti ^{ıv} [equiv.]	Mn [equiv.]	CH ₂ l ₂ [equiv.]	Product (yield) ^[a]
1	0.5	12.8	5	(±)- 3a/3b (1:2; >99 %)
2	0.5	12.8	0	n.r. ^[b]
3	0	12.8	0	n.r. ^[b]
4	0	12.8	5	n.r. ^[b]
5	0.5	0	0	n.r. ^[b]
6	0.5	0	5	n.r. ^[b]

[a] Determined by GC analysis of the crude mixture. [b] n.r. = no reaction.

We went on to study the reaction conditions and the nature of the alkyl halide (Table 2). The reaction of a THF solution of geraniol (1) in the presence of $Cp_2Ti^{III}CI$ was examined with a series of alkyl bromides and iodides at room temperature. We observed that the transesterification reaction did not proceed when alkyl bromides such as CH_2Br_2 and $CHBr_3$ were used (Entries 1, 2, and 4, Table 2).

Table 2. Acetylation of geraniol (1) using different alkyl halides under base-free conditions.

но	geraniol (1)	Cp ₂ T THF, then	iCl ₂ , Mn, alkyl halide, r.t, 2.5 h AcOEt (1.5 h)	0 0 3b
			$\langle 0 \rangle$	
	— () ((±)-+
Entry	Tiv	Mn	Alkyl halide	Product (yield) ^[a]
	[equiv.]	[equiv.]		
1	0.2	8	CH ₂ Br ₂ (5.0 equiv.)	n.r. ^[b]
2	0.2	8	CHBr ₃ (5.0 equiv.)	(±)- 4 (96 %)
3	0.2	8	CH_2I_2 (5.0 equiv.)	(±)- 4 (3 %)
4	0.5	12.8	CHBr ₃ (5.0 equiv.)	(±)- 4 (98 %)
5	0.5	12.8	CH_2I_2 (5.0 equiv.)	(±)- 3a/3b (1:2; >99 %)
6	0.5	12.8	CHI ₃ (5.0 equiv.)	(±)- 4 (99 %)
7	0.5	12.8	l ₂ (5.0 equiv.)	complex mixture

[a] Determined by GC analysis of the crude mixture. [b] n.r. = no reaction.

The results showed not only that the use of CH_2I_2 was essential for a successful reaction, but also that the number of equivalents of both the titanium complex and manganese (compare Entries 3 and 5, Table 2) was crucial. The esterification reaction did not proceed with 0.2 equiv. of titanocene and 8.0 equiv. of manganese (Entry 3, Table 2). The use of different iodide sources such as CHI_3 or I_2 resulted in the formation of (±)-**4** or a complex mixture (Entries 6 and 7, Table 2).

To examine the generality of the procedure, the acetylation conditions were applied to a variety of primary, secondary, and tertiary alcohols, and to phenol, at room temperature. The reaction proceeded quantitatively with aliphatic, benzylic, and allylic primary and secondary alcohols (1 and 5–11; Entries 1–

8, Table 3). It is worth noting that each of the allylic alcohols reacted to give a mixture of the corresponding acetate and the

Table 3. $\mathsf{Cp}_2\mathsf{Ti}^{III}\mathsf{Cl}\text{-catalysed}$ acetylation of alcohols by ethyl acetate under base-free conditions.

	(1) Ср ₂ TiCl ₂ (0.5 е СН ₂ I ₂ (5.0 еqui	O R_↓	
	(2) AcOEt (2.0 equ	iiv.), r.t., 1.5 h	<u>`</u> 0´ <
Entry	Substrate	Product(s)	Yield ^[a]
1	HO~1	AcO (1).3a + (±).3a AcO 3b	(±)- 3a/3b (1:2) (>99%)
2	но	Ac0 ^{-//,} , + (±).16a Ac0 16b	(±)- 16a/16b (1:2) (>99%)
3	HO	AcO	>99%
4	HO 7	AcO 18	>99%
5	HO F	Aco F 19	>99%
6	HO (±)-9	Ac0 (±).20	>99%
7	OH 10		>99%
8		22a 22b	>99% 22a/22b (1.6:1)
9		+ 23a (±).23b	23a (15%) + (±)-23b (15%)
10	OH (+) 13	-	n.r. ^[b]
11	OH 14	-	n.r. ^[b]
12	15	_	n.r. ^(b)

[a] Determined by GC analysis of the crude mixture. [b] n.r. = no reaction.

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim





acetate of the corresponding cyclopropyl derivative (Entries 1, 2, and 8, Table 3). Furthermore, when the reaction was quenched with ethyl acetate under an inert gas after a longer overnight reaction, the acetylated cyclopropyl derivatives [(\pm)-**3a**, (\pm)-**16a**, **22a**] were formed in good yields in a simple onepot reaction (see Supporting Information, S3). Phenol (**15**) and aliphatic tertiary alcohols did not react (Entries 10–12, Table 3), and benzylic tertiary alcohol **12** was converted into the corresponding acetylated product (i.e., **23a**) in low yield, together with its corresponding THF ether (\pm)-**23b** (15 %; Entry 9, Table 3).

Having made this observation, we examined the scope of the transesterification reaction with other ethyl esters. For this purpose, we chose as model substrates a group of primary, secondary, and tertiary alcohols, and phenol [6, (\pm)-9, 14, and 15]. These were subjected to our reaction conditions using ethyl propionate, ethyl butyrate, and ethyl benzoate. Our results showed that 2-phenylethanol (6) was converted into the corresponding propionate (24; 99 % yield) and butyrate (25; 64 % yield) derivatives in good yields (Entries 1 and 2, Table 4), whereas (\pm)-1-phenylethanol [(\pm)-9] gave the propionate [(\pm)-27; 56 % yield] and butyrate [(\pm)-28; 45 % yield] in moderate yields (Entries 4 and 5, Table 4). Ethyl benzoate only reacted

Table 4. $\mathsf{Cp}_2\mathsf{Ti}^{III}\mathsf{Cl}\text{-catalysed}$ transesterification of alcohols under base-free conditions.



[a] Determined by GC analysis of the crude mixture. [b] n.r. = no reaction.

with the primary alcohol (i.e., **6**), giving **26** in low yield (2 %; Entry 3, Table 4). The tertiary alcohol (i.e., **14**) and phenol (**15**) did not react with any of the ethyl esters that were tested (Entries 7 and 8, Table 4). In order to improve the *O*-acylation of tertiary alcohols and phenol, and to extend the reaction to other acyl chains, we then decided to quench the reaction with acyl chlorides.

Alcohols and amines react with acyl chlorides to give esters and amides, respectively, in a reaction known as the Schotten-Baumann reaction.^[9] This reaction requires a nonnucleophilic base, such as pyridine, to be present to obtain high yields. (±)-1-Phenylethanol [(±)-9] was chosen as a model substrate, and subjected to our reaction conditions. Then, the reaction was quenched under an inert gas with valeroyl chloride to give ester (±)-29 in 99 % yield, together with 1,4-iodohydrin 30 (96 % yield based on the acyl chloride; Entry 1, Table 5). In order to explore the O-acylation reaction using an acyl chloride, the role of each reagent was studied. Firstly, we carried out a control reaction between compound (\pm) -9 and valeroyl chloride in THF in the absence of any other reagent (Entry 2, Table 5). Ester (\pm) -29 was only obtained in 50 % yield, in contrast to the 99 % yield obtained when the reaction was carried out under our reaction conditions (Entry 1, Table 5). Similar lower yields were also obtained in the absence of CH_2I_2 , Ti, or Mn (Entries 3–5, Table 5). Finally, compound (±)-29 was obtained in 64 % yield together with 1,4-halohydrin 30 when the reaction was carried out with Mn (12.8 equiv.) and CH₂I₂ (5 equiv.; Entry 6, Table 5).

Table 5. O-Acylation of $(\pm)\textbf{-9}$ with valeroyl chloride under different reaction conditions.

HO (±)- 9	$\frac{(1)}{r.t.,}$	Cp ₂ TiCl ₂ , N 2.5 h valeroyl chl 1.5 h	/In, CH ₂ I ₂ , 1 loride,	THF, O (±)-29
Entry	Ti ^Ⅳ [equiv.]	Mn [equiv.]	CH ₂ l ₂ [equiv.]	Product (yield) ^[a]
1	0.5	12.8	5	(±)- 29 (99 %) + 30 (96 %) ^[b]
2	0	0	0	(±)- 29 (50 %)
3	0.5	12.8	0	(±)- 29 (53 %)
4	0	12.8	0	(±)- 29 (55 %)
5	0.5	0	5	(±)- 29 (50 %)
6	0	12.8	5	(±)- 29 (64 %) + 30 (95 %) ^[b]

[a] Determined by GC analysis of the crude mixture. [b] Yield based on acyl chloride.

Compounds 6, (\pm)-9, 12, 14, and 15 were again chosen as model substrates. These compounds were subjected to our reaction conditions, and the reactions were quenched under an inert gas with valeroyl, pivaloyl, and benzoyl chlorides. Valeroyl chloride reacted with all the tested substrates in excellent yields (84–99%; Entries 1, 4, 7, and 11, Table 6). Benzoyl chloride reacted with 2-phenylethanol (6), (\pm)-1-phenylethanol [(\pm)-9], tertiary alcohol 14, and phenol (15) to give esters 26, (\pm)-34, 38, and 41, respectively, in good yields (78–99%); ester 37 was obtained from 2-phenylpropan-2-ol (12) in moderate yield (Entries 3, 6, 9, 10, and 13, Table 6). Similar results were achieved with pivaloyl chloride, which gave esters 32 and 40 in excellent yields (99 and 91%) from 6 and 15, respectively; ester (\pm)-33





was obtained in moderate yield (61 %) from (\pm)-1-phenylethanol [(\pm)-**9**] (Entries 2, 5, and 12, Table 6). Reaction of pivaloyl chloride with 2-phenylpropan-2-ol (**12**) gave hindered ester **36** in only 20 % yield, together with THF ether (\pm)-**23b**.

When the acyl chlorides used in Tables 5 and 6 were present in excess, the corresponding 1,4-iodohydrins (i.e., **30**, **42**, **43**;

Table 6. Cp₂Ti^{III}Cl-catalysed O-acylation of alcohols and phenol by acyl chlorides under base-free conditions.



[a] Determined by GC analysis of the crude mixture.



Figure 1. 1,4-Halohydrins as by-products in the O-acylation reaction.

In the context of our interest in the study of Ti^{III}-catalysed reactions, we then explored the role of the solvent with the aim of avoiding the formation of the 1,4-halohydrin or cyclopropyl products in the *O*-acylation reaction. Thus, the Cp₂Ti^{III}Cl reagent was generated in dry degassed 1,4-dioxane and tested against a number of alcohols, quenching the reaction under an inert gas with ethyl acetate or acyl chlorides. A solution of **1** together with CH_2I_2 (5 equiv.) was added to the Ti^{III} reagent generated under our reaction conditions in 1,4-dioxane, and the mixture was stirred for 2.5 h.

Surprisingly, when the reaction was quenched with ethyl acetate, geranyl acetate (**3b**) was obtained in a poor 8 % yield. The same experiment was carried out using cinnamyl alcohol (**5**), and cinnamyl acetate (**16b**) was formed in only 9 % yield. None of the cyclopropanation product was observed in either reaction. However, when the reaction of **1** was quenched with pivaloyl, valeroyl, and benzoyl chlorides, the corresponding *O*-acylation products **44–46** (Entries 1–3, Table 7) were obtained quantitatively, and again the corresponding cyclopropyl derivatives were not detected. These results confirm the key role of the solvent in the Ti^{III}-mediated cyclopropanation.^[3]

In order to extend the scope of the *O*-acylation in 1,4-dioxane, model substrates **6**, (\pm)-**9**, **12**, and **15** were tested under our reaction conditions. Benzoyl, valeroyl, and pivaloyl derivatives **26**, **31**, and **32**, were obtained quantitatively from primary alcohol **6** (Entries 4–6, Table 7) when 1,4-dioxane was used as a solvent. This was comparable to the result when the reaction was carried out in THF. A comparable yield was also obtained when secondary alcohol (\pm)-**9** was quenched with pivaloyl chloride (Entry 8, Table 7). In contrast, valeroyl and benzoyl derivatives (\pm)-**29** and (\pm)-**34** were obtained in lower yields than when THF was used as solvent (Entries 7 and 9, Table 7). Lower yields were also observed for the formation of valeroyl, pivaloyl, and benzoyl derivatives from tertiary alcohol **12** and phenol (**15**) (Entries 10–15, Table 7).

A plausible reaction mechanism is shown in Scheme 2, in which the Ti^{III} species is regenerated at various stages by the excess Mn. The mechanism is similar to that described by us for the cyclopropanation reaction of allylic alcohols.^[3] In the light of our results, a related mechanism for the transesterification and *O*-acylation reactions is proposed, in which an activated alkyl/aryloxytitanium species is formed prior to the reaction with esters or acyl chlorides. Coordination of the alcohol to a Ti^{III} species generates complex **A**. A methylene iodide radical generated from methylene diiodide then reacts with complex **A** to give complex **B**. This complex is then reduced by the Mn to give a Ti^{III}-carbenoid species **C**. A direct hydrogen-atom transfer





Table 7. Cp₂Ti^{III}Cl-catalysed O-acylation using 1,4-dioxane as solvent.

(1) Cp ₂ TiCl ₂ (0.5 equiv.)' Mn (12.8 equiv.) 1,4-dioxane, CH ₂ l ₂ (5.0 equiv.), r.t., 2.5 h					
$\begin{array}{c} R \rightarrow OH \\ \hline (2) \text{ acyl chloride, r.t., 1.5 h} \end{array} \qquad $					
Entry	Substrate	Acyl chloride	Product	Yield ^[a]	
1	нолиции нолиции	CI		99%	
2	1	CI		99%	
3	1	CI	BzO 46	98%	
4	HO 6	CI	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	99%	
5	6	CI	40 32	98%	
6	6	CI	BzO 26	98%	
7	HO (±)- 9	∽~~~ ^{CI}	(±).29	48%	
8	(±)- 9	CI	(±)-33	55%	
9	(±)- 9	CI	BzO (±).34	24%	
10	тон 12	CI		43%	
11	12	CI		4%	
12	12	CI	OBz 37	5%	
13	С——ОН 15	CI	<u>ک</u>	39%	
14	15	CI		14%	
15	15	CI	Сровz 41	22%	

[a] Determined by GC analysis of the crude mixture.





(HAT) from alcohol–Ti complex **C** to the iodomethylene radical generates an activated alkyl/aryloxytitanium species.^[12] Quenching of the reaction under an inert gas with either an ester or an acyl chloride then gives the product of transesterification or *O*-acylation, together with species **D**. Coordination of a new alcohol molecule to species **D** then regenerates complex **C** (Scheme 2).



Scheme 2. Proposed mechanism for the formation of the products of transesterification and *O*-acylation.

Conclusions

We have developed a new method for the transesterification and *O*-acylation of alcohols. The method uses substoichiometric amounts of Cp₂Ti^{III}CI with manganese(0) as a reductant together with methylene diiodide in THF, and uses an ethyl ester or acyl chloride as the source of the ester group. Each of these components has been shown to play a key role in the success of the reaction. Esters of primary, secondary, and benzylic alcohols have been obtained under mild conditions in good to excellent yields, both with ethyl esters and with acyl chlorides. The sterically more congested tertiary alcohols gave lower reaction yields. Esters were not obtained from phenol using ethyl esters, due to the delocalization of the phenoxy radical. However, they could be obtained in good yields using acyl chlorides, due to the higher reactivity of the carbonyl carbon atom in these reagents.

Experimental Section

General Methods: Unless otherwise noted, materials and reagents were obtained from commercial suppliers and used without further purification. Tetrahydrofuran and 1,4-dioxane were freshly distilled from Na and strictly deoxygenated under argon for 30 min before use. Ethyl esters and acyl chlorides were not degassed or dried before use. Air- and moisture-sensitive reactions were carried out under argon. Purification by semipreparative and analytical HPLC was carried out with a Hitachi/Merck L-6270 apparatus equipped with a differential refractometer detector (RI-7490). A LiChrospher® Si 60 (5 µm) LiChroCart® (250 mm × 4 mm) column and a LiChrospher® Si 60 (10 µm) LiChroCart® (250 mm × 10 mm) were used in isolation experiments. Silica gel (Merck) was used for column chromatography. TLC was carried out on Merck Kiesegel 60 F254 (0.25 mm thick plates). Reaction yields were determined by GC using a Cyclosil B chiral column. Optical rotations were determined with a digital polarimeter. Infrared spectra were recorded with an FTIR spectrophotometer and are reported as wavenumbers (cm⁻¹). ¹H and ¹³C NMR spectroscopic measurements were recorded with Varian Unity 400 MHz and Agilent 500 MHz spectrometers using SiMe₄ as the internal reference. Chemical shifts were referenced to $CDCl_3$ (δ_H = 7.25 ppm; δ_C = 77.0 ppm). Signals in NMR spectra were assigned using a combination of 1D and 2D techniques. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet; quint = quintuplet; sext = sextuplet; m = multiplet, br. = broad. High-resolution mass spectrometry (HRMS) was carried out with a double-focussing magnetic sector mass spectrometer in positive-ion mode, or with a QTOF mass spectrometer in positive-ion APCI mode or in positive-ion electrospray mode at a 20 V cone voltage.

General Procedure for the Preparation of Esters Mediated by Ti^{III}: A mixture of bis(cyclopentadienyl)titanium dichloride (81.5 mg, 0.32 mmol) and Mn dust (434 mg, 8.19 mmol) in strictly deoxygenated THF or 1,4-dioxane (12.7 mL) under Ar was stirred at room temperature for 15 min. The solution turned green. Then, a solution of the corresponding alcohol (0.64 mmol) and CH_2l_2 (3.2 mmol) in strictly deoxygenated THF or 1,4-dioxane (1.3 mL) was added, and the mixture was stirred for 2.5 h. Then, the corresponding ester or acyl chloride (1.28 mmol) was added under an inert gas, and the reaction mixture was stirred for 1.5 h. The reaction mixture was then filtered through a Celite pad, and the solvent was evaporated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel using mixtures of hexanes and ethyl acetate as eluent to give the corresponding esters.

(±)-(1*R**,2*R**)-2-Methyl-2-(4-methylpent-3-enyl)cyclopropylmethyl Acetate [(±)-3a]: Spectroscopic data for compound (±)-3a are identical to those described in the literature.^[3]

(*E*)-3,7-Dimethylocta-2,6-dienyl Acetate (3b): Spectroscopic data for compound **3b** are identical to those described in the literature.^[13]

(±)-(E)-2-[(3,7-Dimethylocta-2,6-dien-1-yl)oxy]tetrahydrofuran [(±)-4]: Spectroscopic data for compound (±)-4 are identical to those described in the literature.^[4]

(±)-(1*R**,2*R**)-(2-Phenylcyclopropyl)methyl Acetate [(±)-16a]: Spectroscopic data for compound (±)-16a are identical to those described in the literature.^[14]





Cinnamyl Acetate (16b): Spectroscopic data for compound **16b** are identical to those described in the literature.^[15]

Phenethyl Acetate (17): Spectroscopic data for compound **17** are identical to those described in the literature.^[16]

Benzyl Acetate (18): Yellow amorphous solid. IR (film): $\tilde{v} = 3034$, 2940, 1740, 1722, 1454, 1374, 1230, 714, 698 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.37-7.25$ (m, 5 H), 5.10 (s, 2 H), 2.10 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 170.9$, 135.9, 128.5 (2 C), 128.24 (2 C), 128.22, 66.3, 21.0 ppm. HRMS (APCI⁺): calcd. for C₉H₁₁O₂ [M + H]⁺ 151.0759; found 151.0767.

4-Fluorobenzyl Acetate (19): Yellow oil. IR (film): $\tilde{v} = 2953$, 1742, 1606, 1513, 1231 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.33$ (dd, J = 8.7, 5.4 Hz, 2 H), 7.03 (t, J = 8.7 Hz, 2 H), 5.06 (s, 2 H), 2.08 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 170.8$, 162.6 (d, $J_{C,F} = 248$ Hz), 131.8 (d, $J_{C,F} = 3.2$ Hz), 130.2 (d, $J_{C,F} = 8.3$ Hz, 2 C), 115.5 (d, $J_{C,F} = 21.6$ Hz, 2 C), 65.6, 21.0 ppm. HRMS (APCl⁺): calcd. for C₉H₁₀O₂F [M + H]⁺ 169.0665; found 169.0653.

(±)-1-Phenethyl Acetate [(±)-20]: Spectroscopic data for compound (±)-20 are identical to those described in the literature.^[16,17]

(*R*)-Octan-2-yl Acetate (21): Spectroscopic data for compound 21 are identical to those described in the literature.^[18]

(15,2*R***,4***R***,6***R***)-1-Methyl-4-(prop-1-en-2-yl)bicyclo[4.1.0]heptan-2-yl Acetate (22a): Colourless amorphous solid. t_{\rm R} = 24.6 min, petroleum ether/ethyl acetate (99:1), flow = 1.0 mL/min. [α]_D²⁰ = -45.0 (c = 0.1, CHCl₃). IR (film): \tilde{v} = 2943, 1731, 1372, 1242, 1025, 966, 890 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): \delta = 5.21 (dd, J = 11.0, 5.8 Hz, 1 H), 4.62 (m, 2 H), 2.11–2.03 (m, 1 H), 2.07 (s, 3 H), 1.99–1.91 (m, 1 H), 1.83 (ddt, J = 12.2, 5.8, 2.0 Hz, 1 H), 1.64 (s, 3 H), 1.24–1.16 (m, 1 H), 1.07 (s, 3 H), 0.98–0.87 (m, 2 H), 0.54–0.48 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): \delta = 171.3, 148.4, 109.1, 77.2, 41.7, 31.3, 29.9, 24.0, 21.4, 21.2, 20.6, 19.4, 17.9 ppm. HRMS (APCl⁺): calcd. for C₁₃H₂₁O₂ [M + H]⁺ 209.1542; found 209.1541.**

(1*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-enyl Acetate (22b): Colourless amorphous solid. $t_{\rm R}$ = 19.6 min, petroleum ether/ ethyl acetate (99:1), flow = 1.0 mL/min. IR (film): \tilde{v} = 2943, 1731, 1372, 1242, 1025, 966, 890 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 5.59 (m, 1 H), 5.44 (m, 1 H), 4.71 (m, 2 H), 2.34–2.26 (m, 1 H), 2.21– 2.15 (m, 1 H), 2.12–2.04 (m, 1 H), 2.07 (s, 3 H), 2.00–1.90 (m, 2 H), 1.71 (m, 3 H), 1.63 (m, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 171.0, 148.3, 132.8, 125.9, 109.3, 73.2, 40.3, 34.0, 30.8, 21.2, 20.5, 18.8 ppm. HRMS (APCI⁺): calcd. for C₁₂H₁₉O₂ [M + H]⁺ 195.1385; found 195.1377.

2-Phenylpropan-2-yl Acetate (23a): Spectroscopic data for compound **23a** were identical to those described in the literature.^[19]

(±)-2-[(2-Phenylpropan-2-yl)oxy]tetrahydrofuran [(±)-23b]: Spectroscopic data for compound (±)-23b are identical to those described in the literature.^[4]

Phenethyl Propionate (24): Spectroscopic data for compound **24** weare identical to those described in the literature.^[20]

Phenethyl Butyrate (25): Spectroscopic data for compound **25** are identical to those described in the literature.^[21]

Phenethyl Benzoate (26): Spectroscopic data for compound **26** are identical to those described in the literature.^[16]

(±)-1-Phenethyl Propionate [(±)-27]: Spectroscopic data for compound (±)-27 are identical to those described in the literature.^[22]

(±)-1-Phenethyl Butyrate [(±)-28]: Colourless amorphous solid. IR (film): $\tilde{v} = 2966$, 2931, 1736, 1453, 1179, 760, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.35-7.26$ (m, 5 H), 5.89 (q, J = 6.6 Hz, 2 H), 2.31 (t, *J* = 7.4 Hz, 2 H), 1.65 (sext, *J* = 7.4 Hz, 2 H), 1.52 (d, *J* = 6.6 Hz, 3 H), 0.93 (t, *J* = 7.4 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 172.9, 141.8, 128.4 (2 C), 127.8, 126.0 (2 C), 72.0, 36.5, 22.3, 18.4, 13.7 ppm. HRMS (ESI⁺): calcd. for C₁₂H₁₆O₂Na [M + Na]⁺ 215.1048; found 215.1038.

(±)-1-Phenethyl Pentanoate [(±)-29]: Spectroscopic data for compound (±)-29 are identical to those described in the literature.^[23]

4-lodobutyl Pentanoate (30): Spectroscopic data for compound **30** are identical to those described in the literature.^[24]

Phenethyl Pentanoate (31): Colourless amorphous solid. $t_{\rm R}$ = 12.3 min, petroleum ether/ethyl acetate (95:5), flow = 3.0 mL/min. IR (film): \tilde{v} = 2959, 2934, 2873, 1737, 1455, 1251, 1172, 749, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.31–7.20 (m, 5 H), 4.28 (t, *J* = 7.1 Hz, 2 H), 2.93 (t, *J* = 7.1 Hz, 2 H), 2.28 (t, *J* = 7.6 Hz, 2 H), 1.60–1.53 (m, 2 H), 1.35–1.26 (m, 2 H), 0.88 (t, *J* = 7.1 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 173.8, 137.9, 128.9 (2 C), 128.4 (2 C), 126.5, 64.7, 35.1, 34.0, 27.0, 22.2, 13.7 ppm. HRMS (ESI⁺): calcd. for C₁₃H₁₈O₂Na [M + Na]⁺ 229.1204; found 229.1193.

Phenethyl Pivalate (32): Spectroscopic data for compound **32** are identical to those described in the literature.^[25]

(±)-1-Phenethyl Pivalate [(±)-33]: Spectroscopic data for compound (±)-33 are identical to those described in the literature.^[26]

(±)-1-Phenethyl Benzoate [(±)-34]: Spectroscopic data for compound (±)-34 are identical to those described in the literature.^[27]

2-Phenylpropan-2-yl Pentanoate (35): Colourless oil. $t_{\rm R} = 9$ min, petroleum ether/ethyl acetate (95:5), flow = 3.0 mL/min. IR (film): $\tilde{v} = 2959$, 2934, 2873, 1737, 1455, 1251, 1172, 749, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.36-7.20$ (m, 5 H), 2.28 (t, J = 7.5 Hz, 2 H), 1.75 (s, 6 H), 1.62–1.53 (m, 2 H), 1.37–1.28 (m, 2 H), 0.90 (t, J = 7.5 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 172.5$, 146.0, 128.2 (2 C), 126.9, 124.2 (2 C), 81.2, 35.1, 28.6 (2 C), 27.1, 22.2, 13.7 ppm. HRMS (APCI⁺): calcd. for C₁₄H₁₉O₂ [M - H]⁺ 219.1385; found 219.1382.

2-Phenylpropan-2-yl Pivalate (36): Yellow oil. $t_{\rm R}$ = 7.7 min, petroleum ether/ethyl acetate (95:5), flow = 3.0 mL/min. IR (film): \tilde{v} = 2958, 2870, 1726, 1273, 1134 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 7.36–7.23 (m, 5 H), 1.75 (s, 6 H), 1.19 (s, 9 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 176.9, 146.2, 128.2 (2 C), 126.8, 124.1 (2 C), 80.8, 32.9, 28.4 (2 C), 27.1 (3 C) ppm. HRMS (APCI⁺): calcd. for C₁₄H₂₁O₂ [M + H]⁺ 221.1545; found 221.1542.

2-Phenylpropan-2-yl Benzoate (37): Yellow oil. $t_{\rm R} = 11.2$ min, petroleum ether/ethyl acetate (95:5), flow = 3.0 mL/min. IR (film): $\tilde{v} = 2981$, 1720, 1450, 1314, 1282, 1112, 1098, 712, 699 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): $\delta = 8.04$ (m, 2 H), 7.54 (m, 1 H), 7.43 (m, 4 H), 7.33 (m, 2 H), 7.26 (m, 1 H), 1.92 (s, 6 H) ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 165.1$, 145.8, 132.7, 131.5, 129.5 (2 C), 128.33 (2 C), 128.26 (2 C), 127.0, 124.3 (2 C), 82.2, 28.8 (2 C) ppm. HRMS (APCl⁺): calcd. for C₁₆H₁₅O₂ [M – H]⁺ 239.1072; found 239.1069.

2,4,6-Trimethylhepta-1,6-dien-4-yl Benzoate (38): Colourless oil. $t_{\rm R} = 6.5$ min, petroleum ether/ethyl acetate (97:3), flow = 3.0 mL/ min. IR (film): $\tilde{v} = 2969$, 2946, 1714, 1644, 1450, 1375, 1314, 1278, 1244, 1115, 1082, 710 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): $\delta = 7.99-$ 7.97 (dd, J = 8.0, 1.0 Hz, 2 H), 7.54–7.51 (t, J = 8.0 Hz, 1 H), 7.41 (t, J = 8.0 Hz, 2 H), 4.88 (s, 2 H), 4.76 (s, 2 H), 2.84 (d, J = 14.5 Hz, 2 H), 2.61 (d, J = 14.5 Hz, 2 H), 1.78 (s, 6 H), 1.57 (s, 3 H) ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 165.9$, 141.8 (2 C), 132.5, 131.9, 129.4 (2 C), 128.3 (2 C), 115.5 (2 C), 84.7, 46.7 (2 C), 24.2 (3 C) ppm. HRMS (APCI⁺): calcd. for C₁₇H₂₁O₂ [M – H]⁺ 257.1542; found 257.1534.

Phenyl Pentanoate (39): Spectroscopic data for compound **39** are identical to those described in the literature.^[28]





Phenyl Pivalate (40): Spectroscopic data for compound **40** are identical to those described in the literature.^[28]

Phenyl Benzoate (41): Spectroscopic data for compound **41** are identical to those described in the literature.^[28,29]

4-Iodobutyl Pivalate (42): Spectroscopic data for compound **42** are identical to those described in the literature.^[24]

4-Iodobutyl Benzoate (43): Spectroscopic data for compound **43** are identical to those described in the literature.^[30]

(*E*)-3,7-Dimethylocta-2,6-dienyl Pentanoate (44): Yellow oil. $t_{\rm R}$ = 6 min, petroleum ether/ethyl acetate (95:5), flow = 3.0 mL/min. IR (film): \tilde{v} = 2962, 2931, 2874, 1736, 1450, 1380, 1171 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 5.34 (t, *J* = 7.0 Hz, 1 H), 5.08 (t, *J* = 7.0 Hz, 1 H), 4.58 (d, *J* = 7.0 Hz, 2 H), 2.30 (t, *J* = 7.0 Hz, 2 H), 2.11–2.02 (m, 4 H), 1.70 (s, 3 H), 1.68 (s, 3 H), 1.64–1.58 (m, 2 H), 1.60 (s, 3 H), 1.35 (sept, *J* = 7.5 Hz, 2 H), 0.91 (t, *J* = 7.5 Hz, 3 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 173.9, 142.1, 131.8, 123.8, 118.4, 61.2, 39.5, 34.1, 27.1, 26.3, 25.7, 22.3, 17.7, 16.4, 13.7 ppm. HRMS (APCl⁺): calcd. for C₁₅H₂₇O₂ [M + H]⁺ 239.2011; found 239.2018.

(*E*)-3,7-Dimethylocta-2,6-dienyl Pivalate (45): Spectroscopic data for compound 45 are identical to those described in the literature.^[31]

(E)-3,7-Dimethylocta-2,6-dienyl Benzoate (46): Spectroscopic data for compound **46** are identical to those described in the literature.^[32]

Acknowledgments

This research was supported by a grant from the Ministerio de Economía y Competitividad (AGL2015-65684-C2-1-R and BFU2015-68652-R) (MINECO-FEDER). M. J. D.-P. acknowledges the award of a Contrato Puente para Doctores supported by the University of Cádiz. The use of the NMR facilities at the Servicio Centralizado de Ciencia y Tecnología (SCCYT) of the University of Cádiz is acknowledged.

Keywords: Esters · Acylation · Radical reactions · Halohydrins · Titanium

- [1] a) T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley and Sons, New York, **1999**; b) R. C. Larock, Comprehensive Organic Transformations, VCH, New York, **1989**, p. 966.
- [2] a) S. K. Prajapti, A. Nagarsenkar, B. N. Babu, *Tetrahedron Lett.* 2014, *55*, 910–912; b) Z. Liu, Q. Ma, Y. Liu, Q. Wang, *Org. Lett.* 2014, *16*, 236–239; c) T. N. Parac-Vogt, K. Deleersnyder, K. Binnemans, *Eur. J. Org. Chem.* 2005, *9*, 1810–1815; d) C. T. Chen, J. H. Kuo, V. D. Pawar, Y. S. Munot, S. S. Weng, C. H. Ku, C. Y. Liu, *J. Org. Chem.* 2005, *70*, 1188; e) A. Tai, S. S. Kulkarni, S. C. Hung, *J. Org. Chem.* 2003, *68*, 8719; f) T. Sano, K. Ohashi, T. Oriyama, *Synthesis* 1999, *7*, 1141–1144.
- [3] M. J. Durán-Peña, J. M. Botubol-Ares, J. R. Hanson, R. Hernández-Galán, I. G. Collado, Org. Biomol. Chem. 2015, 13, 6325–6332.
- [4] M. J. Durán-Peña, J. M. Botubol-Ares, J. R. Hanson, R. Hernández-Galán, I. G. Collado, *Eur. J. Org. Chem.* **2015**, 6333–6340.
- [5] For pioneering reports on the use of this reagent, see: T. V. RajanBabu, W. A. Nugent, J. Am. Chem. Soc. **1994**, 116, 986–997, and references cited therein.
- [6] a) H. R. Dieguez, A. Lopez, V. Domingo, J. F. Arteaga, J. A. Dobado, M. M. Herrador, J. F. Quilez del Moral, A. F. Barrero, J. Am. Chem. Soc. 2010, 132,

254–259; b) J. M. Cuerva, A. G. Campana, J. Justicia, A. Rosales, J. L. Oller-Lopez, R. Robles, D. J. Cardenas, E. Bunuel, J. E. Oltra, *Angew. Chem. Int. Ed.* **2006**, *45*, 5522–5526; *Angew. Chem.* **2006**, *118*, 5648–5652.

- [7] a) A. Rosales, I. Rodriguez-Garcia, J. Muñoz-Bascon, E. Roldan-Molina, N. M. Padial, L. P. Morales, M. Garcia-Ocaña, J. E. Oltra, *Eur. J. Org. Chem.* **2015**, 4567–4591; b) S. P. Morcillo, D. Miguel, A. G. Campaña, L. Álvarez de Cienfuegos, J. Justicia, J. M. Cuerva, *Org. Chem. Front.* **2014**, *1*, 15–33 and references cited therein; c) A. Gansäuer, J. Justicia, C.-A. Fan, D. Worgull, F. Piestert, *Top. Curr. Chem.* **2007**, *279*, 25–52; d) J. M. Cuerva, J. Justicia, J. L. Oller-López, J. E. Oltra, *Top. Curr. Chem.* **2006**, *264*, 63–91; e) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771–2788.
- [8] a) A. Rosales, J. Muñoz-Bascon, C. Lopez-Sanchez, M. Alvarez-Corral, M. Muñoz-Dorado, I. Rodriguez-Garcia, J. E. Oltra, J. Org. Chem. 2012, 77, 4171–4176; b) A. F. Barrero, M. M. Herrador, J. F. Quilez del Moral, P. Arteaga, M. Akssira, F. El Hanbali, J. F. Arteaga, H. R. Dieguez, E. M. Sanchez, J. Org. Chem. 2007, 72, 2251–2254; c) A. Gansäuer, H. Bluhm, M. Pierobon, J. Am. Chem. Soc. 1998, 120, 12849–12859.
- [9] L. Kürti, C. Barbara, Strategic Applications of Named Reactions in Organic Synthesis, Elsevier Academic Press, London, 2005, p. 398.
- [10] Yields based on the amount of acyl chloride added.
- [11] Work is in progress to study the scope and limitations of this method for the synthesis of 1,4-halohydrins and their derivatives.
- [12] M. Paradas, A. G. Campaña, T. Jiménez, R. Robles, J. E. Oltra, E. Buñuel, J. Justicia, D. J. Cárdenas, J. M. Cuervas, J. Am. Chem. Soc. 2010, 132, 12748–12756.
- [13] a) B. M. Smith, E. J. Skellam, S. J. Oxley, A. E. Graham, Org. Biomol. Chem. 2007, 5, 1979–1982; b) K. Surendra, E. J. Corey, J. Am. Chem. Soc. 2008, 130, 8865–8869.
- [14] J. Pietruszka, A. C. M. Rieche, T. Wilhelm, A. Witt, Adv. Synt. Catal. 2003, 345, 1273–1286.
- [15] J.-L. Debieux, A. Cosandey, C. Helgen, C. G. Bochet, Eur. J. Org. Chem. 2007, 2073–2077.
- [16] S. Magens, M. Ertelt, A. Jatsch, B. Plietker, Org. Lett. 2008, 10, 53–56.
- [17] A. K. Chakraborti, S. V. Chankeshwara, J. Org. Chem. 2009, 74, 1367–1370.
- [18] M. Maywald, A. Pfaltz, Synthesis 2009, 31, 3654–3660.
- [19] M. Hatano, Y. Furuya, T. Shimmura, K. Moriyama, S. Kamiya, T. Maki, K. Ishihara, Org. Lett. 2011, 13, 426–429.
- [20] J. McNulty, J. J. Nair, S. Cheekoori, V. Larichev, A. Capretta, A. J. Robertson, *Chem. Eur. J.* **2006**, *12*, 9314–9322.
- [21] a) S.-S. Weng, C.-S. Ke, F. K. Chen, Y.-F. Lyu, G.-Y. Lin, *Tetrahedron* 2011, 67, 1640–1648; b) C.-T. Chen, J.-H. Kuo, V. D. Pawar, Y. S. Munot, S.-S. Weng, C.-H. Ku, C.-Y. Liu, *J. Org. Chem.* 2005, 70, 1188–1197.
- [22] M. Barbero, S. Cadamuro, S. Dughera, P. Venturello, Synthesis 2008, 3625– 3632.
- [23] G. Xu, Y. Chen, J. Wu, Y. Cheng, L. Yang, *Tetrahedron: Asymmetry* 2011, 22, 1373–1378.
- [24] K. Venkatesham, D. C. Babu, T. V. Bharadwaj, R. A. Bunce, C. B. Rao, Y. Venkateswarlu, *RSC Adv.* **2014**, *4*, 51991–51994.
- [25] C. B. Rao, Ch. B. Chinnababu, Y. J. Venkateswarlu, J. Org. Chem. 2009, 74, 8856–8858.
- [26] R. Chenevert, N. Pelchat, P. Morin, *Tetrahedron: Asymmetry* 2009, 20, 1191–1196.
- [27] T. Ohshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama, K. Mashima, J. Am. Chem. Soc. 2008, 130, 2944–2945.
- [28] T. Shinntou, K. Fukumoto, T. Mukaiyama, Bull. Chem. Soc. Jpn. 2004, 77, 1569–1579.
- [29] a) S. Gemming, M. Lehmann, G. Seifert, Z. Metallkd. 2005, 96, 988–997;
 b) C. K. Lee, J. S. Yu, H.-J. Lee, J. Heterocycl. Chem. 2002, 39, 1207–1217.
- [30] M. M. Ott, R. D. Little, J. Org. Chem. **1997**, 62, 1610–1616.
- [31] B. M. Smith, E. J. Skellam, S. J. Oxley, A. E. Graham, Org. Biomol. Chem. 2007, 5, 1979–1982.
- [32] M. Hatano, Y. Furuya, T. Shimmura, K. Moriyama, S. Kamiya, T. Maki, K. Ishihara, Org. Lett. 2011, 13, 426–429.

Received: April 20, 2016 Published Online: July 4, 2016