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Unusual reaction of allylic systems: homo- and cross-cyclizations leading to four-carbon rings

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ABSTRACT

The reaction of stabilized allylic-type carbocations with electron rich olefins was investigated. In most cases a facile cyclobutane ring formation was observed by [2+2] cycloaddition reaction promoted by Brønsted or Lewis acids. Some attempts were made to investigate the mechanistic pathway. After de-racemization the chiral cyclobutane containing diols were obtained as a potential chiral platform for new ligands.

1. Introduction

Syntheses of the cyclobutane system have gained remarkable importance in the synthesis of natural products and other compounds of biological significance.[1,2] The principal strategies for their synthesis are based on [2+2] photochemical or catalytic cycloaddition, 1,4-cyclization of acyclic precursors and a ring expansion of cyclopropanes.[1,3] Cationic [2+2] cycloadditions employing simple allylic compounds for the preparation of cyclobutanes are not often represented, though that pathway has a biosynthetic origin.[4] The literature reported relevant examples,[5] and mostly the reactions of enol ethers[6] or silyl enol ethers,[7] vinyl acetals[8] or allylsilanes[9,10] with olefins or α,β-unsaturated carbonyl compounds were exploited for this purpose.

2. Results and discussion

During our recent work dealing with allylic alcohols, we have found an unusual reaction leading to the formation of the four-carbon ring system. The treatment of 1,3-diphenyl-2-propen-1-ol (**1**) with acetic anhydride in the presence of catalytic sulfuric acid, instead of the expected allylic acetate furnished the head-to-tail dimer (Fig. 1). The product was identified as 1,3-diphenyl-2,4-bis-[α-acetoxy-benzyl]-cyclobutane **5a** (60% yield, **5b** <5%) with all groups tethered to the cyclobutane ring in trans positions.

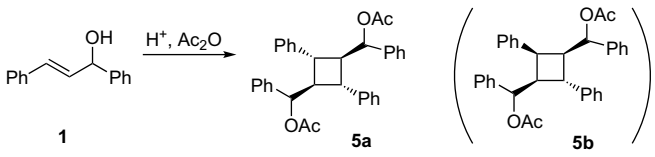

Figure 1.

A similar dimerization of **1** in the presence of HBr has already been observed by Staab and Kurmeier in 1968.[11] To the best of our knowledge, this observation was neglected for the next 40 years with no published further investigation nor application of this reaction. Spectral properties of **5a** were in agreement with those already reported. Its *all-trans* geometry was proved by chemical correlation with ε-truxilic acid (derivative of natural alkaloid).[11] Additionally, the ^{1}H NMR spectrum of **5a** in the presence of Eu(hfc)$_3$ revealed the splitting of OCOCH_3 signal ($\Delta\delta$=0.06 ppm), that corresponds with equimolar amounts of two enantiomers (*R*,*R*) and (*S*,*S*); no *meso* form has been observed. The reaction can be considered formally as the ionic [2+2] cycloaddition with the allylic system. The use of dichloromethane as a solvent decreased the selectivity keeping the chemical yield almost unchanged. Thus, along with the *all-trans* product **5a** (27%), its stereoisomer **5b** was isolated (30%). The geometry of this isomer was established using ^{1}H NMR. The signal from the *o*-protons of the phenyl ring in the cis-position to the acetoxy groups was considerably shifted to the higher field. The significant effect of cyclobutane proton differentiation was also clearly seen. This observed homo-dimerization prompted us to examine the corresponding cross-cyclization. Thus, several olefins were reacted with **1** under the same conditions (Fig. 2). The reactions gave products of [2+2] cycloaddition (see Table 1) together with the products of homo-cyclization (**5a**+**5b**).

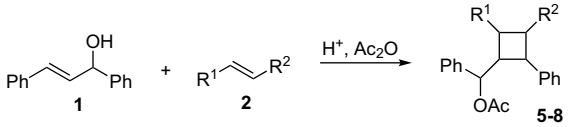

Figure 2.

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Table 1
Cyclization of **1** with different olefins **2**

2	R^1, R^2	Product[a]	Yield[b] (%)
a	R^1=Ph, R^2=CH(OH)Ph	**5**	65
b	R^1=R^2=Ph	**6**	40
c	R^1=Ph, R^2=H	**7**	50
d	R^1=C(CH_3)=CH_2, R^2=H	**8**	30

[a] Products of cross-cyclization were obtained together with **5a**+**5b**.
[b] Yields of isolated compounds.

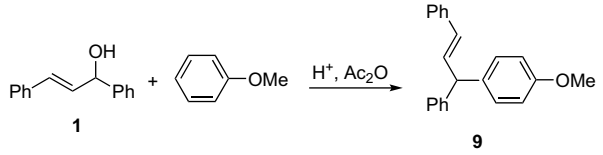


Figure 3.

The stereochemistry of **6**, the main product of the cross-reaction with *trans*-stilbene, was defined on the basis of ^{1}H NMR also as *all-trans*. The formation of the second isomer was also observed (less then 10% by NMR), but it could not be isolated as a pure compound. The geometry of other products (**7** and **8**) was not established. Beside **5a** all the obtained cyclobutane derivatives were hitherto unknown. In the case of norbornene the cycloaddition did not occur and solely the product of esterification of **1** was isolated (63%).

In experiments designed to gain information about the mechanism of this process, we first attempted to detect the reaction intermediate. The addition of anisole (1 equiv) to the reaction mixture (Fig. 3) resulted in the formation of the typical product of electrophilic allylation **9**[12] (65%) along with **5** (20%). This result suggests the formation of carbocation during the reaction pathway.

Also the reaction of **1** with 3,4-dihydro-2*H*-pyran, well known as a 'trapping agent' for carbocations, in the same conditions led to compound **10**, being the product of allylation (Fig. 4). This result supported our conclusion about carbocation formation in this reaction.

We have also made an experiment with the deuterated alcohol **11**, obtained by $LiAlD_4$ reduction of chalcone (Fig. 5).

In the ^{1}H NMR spectrum of obtained product **12** we observed decreasing by half an integration of signals from all protons at the benzylic positions (two from cyclobutane ring (m, 3.00–3.07 ppm) and two close to the acetyl groups (d, 5.85 ppm)). It suggests that before the cyclization the delocalized allylic carbocation has been formed.

It should be noted that there is no evidence to suggest, which process is faster: carbocation formation or acetylation of allyl alcohol. To answer this question we used the corresponding allyl acetate as a substrate for the dimerization. The results were similar to those obtained with alcohol **1** itself, namely the yield was slightly better, but the selectivity was worse (51% **5a**, 34% **5b**). A plausible stepwise mechanism for the [2+2] cycloaddition with allylic carbocation is depicted in Scheme 1. In the first step the formation of allylic cation takes place (fast process), followed by the addition reaction to the double bond of the second molecule. The newly formed carbocation **3** can cyclize to the cyclobutane ring **4** via the second addition stage. The ensuing acetylation gives the final product (**5**–**8**). It seems that the reaction stereoselectivity would be determined in the second addition step.

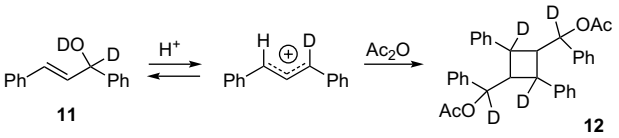


Figure 5.

In order to check briefly the scope and limitations the other acids have been applied for generation of allyl cations in the homo-cyclization reaction. As summarized in Table 2, the Lewis acids (except $TiCl_4$) appeared to be useful and gave **5** in even better yield as compared to sulfuric acid. However, the stereoselectivity was slightly lower in those cases.

We have also tested the homo-dimerization with 3-phenyl-2-propen-1-ol (**13**) as a substrate. However, in this case only the first stage of the described process (Scheme 1) took place. The benzyl carbocation corresponding to **3** (see Scheme 1, R^1=Ph, R^2=CH_2OH), obtained after the first addition seems to be quenched with acetic acid faster then the cyclization occurs. The corresponding product (2-(α-acetoxy-benzyl)-5-phenylpent-4-enyl acetate, **14**) was isolated as a mixture of two diastereoisomers (2:1, 30% yield) next to cinnamyl acetate (Fig. 6).

Although compound **5a** was obtained as a racemate, it seemed interesting because of its rigid structure and well defined geometry (*all-trans*) around the cyclobutane ring. We reacted the racemic diol (**15**), obtained after the hydrolysis of **5a**, with (*R*)-*O*-methylatrolactic acid[13] used as a resolving agent (Scheme 2). The respective enantiomeric diols gave monoesters: **16a** and **16b**, along with bisester **17a** (formed much faster than isomer **17b**), all separable by \column chromatography. After the hydrolysis of separated mono- and bisesters it was possible to isolate the enriched (+)- and (−)-isomers of (2,4-diphenyl-cyclobutane-1,3-diyl)bis(phenyl-methanol)-**15**. In the case of (+)-**15** obtained from **16a** the ee was 85% whereas from **17a**, the ee was 95% (confirmed by HPLC). Thus, this esterification allows for the substantial enantiomeric enrichment of the isolated products. Diols (**15**) offer a promising chiral platform for the construction of new chiral ligands and further investigations in this direction are underway.

3. Conclusion

The cationic [2+2] cycloaddition with allylic system generated in the presence of Brønsted or Lewis acid was investigated. Several new cyclobutane derivatives were obtained as the products of homo- or cross-cyclization. The stepwise mechanism involving the carbocation formation followed by its addition to the double bond and the final cyclization was proposed. The sequential esterification with the resolving acid followed by hydrolysis allowed for the separation of racemic diol **15**.

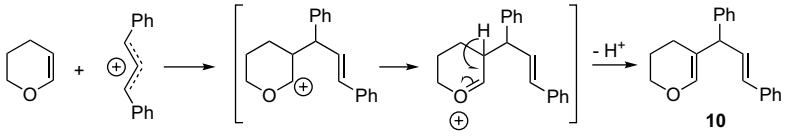
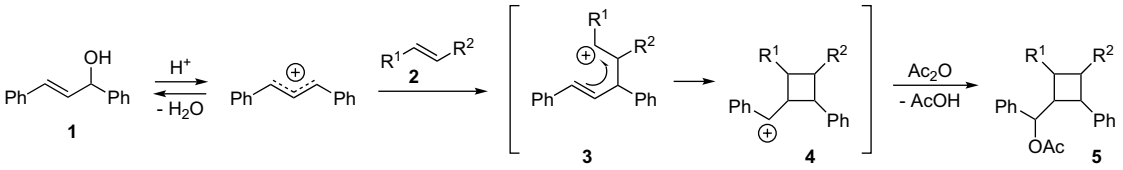


Figure 4.



Scheme 1. Postulated mechanism of cyclization.

Table 2
Application of different acids as catalysts in homo-dimerization of **1**

Substrate	Acid	Yield[a] (%)	
		5a	**5b**
1	H_2SO_4	65	<5[b]
1	$SnCl_4$	70	20
1	$BF_3 \cdot Et_2O$	82	14
1	$TiCl_4$	28	21
1	*p*-TsOH	5[b]	7[b]

[a] Yields of isolated compounds.
[b] Yields calculated from the ^1H NMR spectrum.

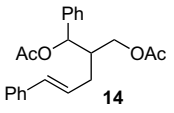


Figure 6.

4. Experimental part

Commercially available reagents and solvents were used except the (*R*)-*O*-methylatrolactic acid. Separation of products by chromatography was performed on silica gel 60 (230–400 mesh) purchased from Fluka. Melting points are uncorrected. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ or DMSO were recorded on Bruker Avance DRX (^1H, 300 MHz) spectrometer, using TMS as an internal standard. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer. The high-resolution mass spectra (HRMS) were recorded on a Mariner PE Biosystems unit. Observed rotations at 589 nm were measured using an Optical Activity Ltd Model AA-5 automatic polarimeter.

4.1. General procedure of cyclization

To a solution of **2** (3 mmol) in 3 mL of acetic anhydride a few drops of concd H_2SO_4 (~2%) was added. Then the allylic alcohol **1** (3 mmol) was added in portions and the mixture was stirred (temp <20 °C) for 2 h. A strong coloration (mostly red) was observed during the reaction. After that time the reaction mixture was poured into the ice–water mixture, neutralized with 1 M NaOH and extracted with dichloromethane. The organic solution was dried (Na_2SO_4 anhyd) and evaporated in vacuo. The product was isolated after column chromatography (silica gel; AcOEt/hexane, 1:5 v/v).

4.2. Analytical data of obtained products

*4.2.1. all-trans-1,3-Diphenyl-2,4-bis-[α-acetoxy-benzyl]-cyclobutane (**5a**)*

White crystals, mp 167–170 °C (toluene); R_f (AcOEt/hexane, 1:5) 0.42; δ_H (300 MHz, $CDCl_3$): 1.76 (s, 6H, CH_3), 2.91–2.97 (m, 2H, CH), 3.00–3.07 (m, 2H, CH), 5.92 (d, 2H, *J* 6.8 Hz, CH), 7.01 (dd, 4H, *J* 6.6, 1.5 Hz, ArH), 7.08–7.13 (m, 16H, ArH); δ_C (300 MHz, $CDCl_3$): 20.9, 42.7, 51.8, 77.5, 126.2, 127.1, 127.2, 128.0, 128.1, 128.2, 137.6, 141.9, 170.3; ν_{max} (KBr): 3063, 3030, 2932, 2917, 1734, 1496, 1456, 1369, 1248, 1024, 756, 696; HRMS (ESI, MeOH): $[M+Na]^+$ calcd for $C_{34}H_{32}O_4Na$: 527.21928, found: 527.22183.

*4.2.2. cis,trans,trans-1,3-Diphenyl-2,4-bis-[α-acetoxy-benzyl]-cyclobutane (**5b**)*

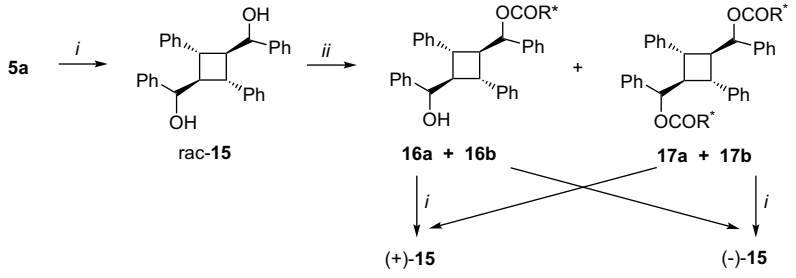
White crystals, mp 140–142 °C (EtOH); R_f (AcOEt/hexane, 1:5) 0.37; δ_H (300 MHz, $CDCl_3$): 1.81 (s, 6H, CH_3), 2.91–2.93 (m, 3H, CH), 3.13–3.18 (m, 1H, CH), 5.89 (d, 2H, *J* 5.7 Hz), 6.87 (dd, 2H, *J* 7.5, 1.8 Hz, ArH), 7.04–7.26 (m, 18H, ArH); δ_C (300 MHz, $CDCl_3$): 20.9, 41.4, 44.0, 51.9, 77.4, 126.1, 126.4, 127.0, 127.1, 127.2, 127.4, 128.0, 128.2, 128.3, 137.7, 141.4, 142.4, 170.2; ν_{max} (KBr): 3086, 3059, 3027, 3005, 2932, 1745, 1723, 1495, 1457, 1249, 1235, 1024, 760, 696; HRMS (ESI, MeOH): $[M+Na]^+$ calcd for $C_{34}H_{32}O_4Na$: 527.21928, found: 527.22127.

*4.2.3. all-trans-Phenyl(2,3,4-triphenylcyclobutyl)methyl acetate (**6**)*

White solid, mp 108–110 °C (hexane); R_f (AcOEt/hexane, 1:5) 0.44; δ_H (300 MHz, $CDCl_3$): 1.88 (s, 3H, CH_3), 3.13 (ddd, 1H, *J* 6.9, 9.3, 9.3 Hz, CH), 3.30 (t, 1H, *J* 9.3 Hz, CH), 3.44 (t, 1H, *J* 9.3 Hz, CH), 3.53 (t, 1H, *J* 9.3 Hz, CH), 6.09 (d, 1H, *J* 6.9, CH), 7.05–7.32 (m, 20H, ArH); δ_C (300 MHz, $CDCl_3$): 21.1, 46.9, 48.1, 51.2, 52.5, 78.1, 126.4, 126.6, 126.6, 126.9, 127.2, 127.2, 127.3, 128.1, 128.3, 128.3, 128.5, 128.5, 138.0, 142.0, 142.5, 142.6, 170.3; ν_{max} (KBr): 3083, 3061, 3027, 2934, 1733, 1494, 1229, 1026, 769, 699; HRMS (ESI, MeOH): $[M+Na]^+$ calcd for $C_{31}H_{28}O_2Na$: 455.1982, found: 455.1965.

*4.2.4. (2,3-Diphenylcyclobutyl)(phenyl)methyl acetate (**7**)*

Oil, mixture of two stereoisomers (65%:35%); R_f (AcOEt/hexane, 1:5) 0.45; δ_H (300 MHz, $CDCl_3$): 2.02 (s, 65% 3H, CH_3), 2.04 (s, 35%



Scheme 2. (i) LiOH, MeOH, reflux, 3 h; (ii) R'COOH, DCC, CH_2Cl_2, rt, 5 days.

3H, CH_3), 2.23–2.32 (m, 1H, CH_AH_B), 2.48–2.58 (m, 1H, CH_AH_B), 3.42–3.49 (m, 1H, CH), 5.65–5.70 (m, 35% 1H, CH), 5.71–5.76 (m, 65% 1H, CH), 6. 31(d, 1H, *J* 7.2 Hz, CH–O), 6.34–6.41 (m, 1H. CH), 7.24–7.36 (m, 15H, ArH); δ_C (300 MHz, $CDCl_3$): 65% 21.3, 35% 21.4, 65% 42.1, 35% 42.2, 45.9, 74.6, 76.3, 126.4, 126.8, 126.9, 127.4, 127.7, 127.8, 128.2, 35% 128.6, 65% 128.7, 65% 128.9, 35% 128.9, 35% 130.0, 65% 130.2, 35% 133.0, 65% 133.2, 65% 137.3, 35% 137.4, 140.6, 65% 143.2, 35% 143.4, 170.2; ν_{max} (CCl_4): 3086, 3065, 3031, 2937, 1741, 1495, 1454, 1371, 1237, 1026, 965; HRMS (ESI, MeOH): $[M+Na]^+$ calcd for $C_{25}H_{24}O_2Na$: 379.1669, found: 379.1665.

*4.2.5. Phenyl(2-phenyl-4-(prop-1-en-2-yl)cyclobutyl)methyl acetate (**8**)*

Oil, equimolar mixture of two stereoisomers; R_f (AcOEt/hexane, 1:5) 0.47; δ_H (300 MHz, $CDCl_3$): 1.72 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.08–2.13(m, 1H, CH_AH_B), 2.22–2.25 (m, 1H, CH_AH_B), 2.54–2.56 (m, 1H, CH), 3.62–3.70 (m, 2H, 2×CH), 4.49 (br d, 2H, *J* 6.5 Hz, CH_2), 5.74–5.78 (m, 1H, CHOAc), 7.21–7.42 (m, 10H, ArH); δ_C (300 MHz, $CDCl_3$): 21.3, 21.3, 21.4, 21.4, 39.8, 40.1, 41.8, 46.8, 46.9, 76.3, 79.7, 110.7, 126.4, 126.6, 128.3, 128.4, 128.7, 130.1, 130.2, 140.1, 140.2, 141.3, 141.6, 147.0, 170.2; ν_{max} (CCl_4): 3085, 3064, 3029, 2934, 1741, 1495, 1453, 1367, 1233, 1029, 964; HRMS (ESI, MeOH): $[M+K]^+$ calcd for $C_{22}H_{24}O_2K$: 359.1408, found: 359.1598.

*4.2.6. 1,3-Diphenyl-1-(4-methoxyphenyl)prop-2-ene (**9**)*

Oil, R_f (AcOEt/hexane, 1:5) 0.47; δ_H (300 MHz, $CDCl_3$): 3.80 (s, 3H, CH_3), 4.86 (d, 1H, *J* 7.5 Hz, CH), 6.34 (d, 1H, *J* 15.9 Hz, CH), 6.67 (dd, 1H, *J* 15.9, 7.5 Hz, CH), 6.87 (d, 2H, *J* 8.7 Hz, ArH), 7.16 (d, 2H, *J* 8.7 Hz, ArH), 7.23–7.42 (m, 10H, ArH); δ_C (300 MHz, $CDCl_3$): 53.5, 55.4, 114.0, 126.5, 126.6, 127.5, 128.7, 128.7, 128.8, 129.8, 131.4, 133.1, 135.8, 137.5, 144.0, 158.3; In agreement with data reported in the literature.[12]

*4.2.7. (E)-5-(1,3-Diphenylallyl)-3,4-dihydro-2H-pyran (**10**)*

Oil, R_f (AcOEt/hexane, 1:5) 0.67; δ_H (300 MHz, $CDCl_3$): 1.86–1.92 (m, 4H, 2×CH_2), 3.97 (t, 2H, *J* 5.0 Hz, CH_2), 4.05 (d, 1H, *J* 6.9 Hz, CH), 6.40 (d, 1H, *J* 15.9 Hz, CH), 6.44 (s, 1H, CH), 6.51 (dd, 1H, *J* 15.9, 6.9 Hz, CH), 7.24–7.44 (m, 10H, ArH); δ_C (300 MHz, $CDCl_3$): 22.4, 22.7, 52.3, 65.6, 114.7, 126.3, 126.5, 127.3, 128.4, 128.5, 128.6, 131.0, 131.4, 137.5, 141.5, 142.5; ν_{max} (CCl_4): 3083, 3062, 3028, 2971, 2948, 2931, 2895, 1661, 1494, 1150, 967, 700; HRMS (EI): $[M^+]$ calcd for $C_{20}H_{20}O$: 276.15142, found: 276.15210.

*4.2.8. 2-(α-Acetoxy-benzyl)-5-phenylpent-4-enyl acetate (**14**)*

Oil, mixture of two diastereoisomers (2:1), R_f (AcOEt/hexane, 1:5) 0.41; δ_H (300 MHz, $CDCl_3$): 2.01 (s, 1/3 3H, CH_3), 2.03 (s, 2/3 3H, CH_3), 2.08 (s, 2/3 3H, CH_3), 2.11 (s, 1/3 3H, CH_3), 2.14–2.21 (m, 1H, CH_AH_B), 2.32–2.39 (m, 2H, CH_AH_B, CH), 3.85 (dd, 1/3 1H, *J* 11.4, 5.4 Hz, CH_AH_B), 4.05–4.12 (m 1H, CH_AH_B), 4.30 (dd, 2/3 1H, *J* 11.4, 5.4 Hz, CH_AH_B), 5.83 (d, 2/3 1H, *J* 7.5 Hz, CH), 5.89 (d, 1/3 1H, *J* 6.3 Hz, CH), 6.03–6.18 (m, 1H, CH), 6.32 (d, 2/3 1H, *J* 15.5 Hz, CH), 6.39 (d, 1/3 1H, *J* 15.6 Hz, CH), 7.20–7.39 (m, 10H, ArH); δ_C (300 MHz, $CDCl_3$): 1/3 20.9, 2/3 21.0, 21.2, 1/3 31.0, 2/3 31.5, 2/3 43.3, 1/3 43.4, 2/3 62.8, 1/3 63.5, 2/3 75.4, 1/3 75.5, 126.1, 126.7, 126.8, 127.1, 127.3, 1/3 128.2, 2/3 128.3, 128.6, 1/3 132.3, 2/3 132.6, 2/3 137.3, 1/3 137.3, 2/3 138.7, 1/3 138.8, 2/3 170.0, 1/3 170.1, 1/3 170.9, 2/3 171.0; ν_{max} (film): 3082, 3061, 3029, 2956, 1740, 1496, 1451, 1370, 1236, 1026, 967, 745, 701; HRMS (ESI, MeOH): $[M+NH_4]^+$ calcd for $C_{22}H_{28}O_4N$: 370.2013, found: 370.2008.

*4.2.9. (2,4-Diphenyl-cyclobutane-1,3-diyl)bis(phenylmethanol) (**15**)*

White solid, mp 198–200 °C (toluene); R_f (AcOEt/hexane, 1:3) 0.15; δ_H (300 MHz, $CDCl_3$): 2.00 (br s, 2H, OH), 2.78 (ddd, 2H, *J* 5.4, 8.7, 8.7 Hz, CH), 3.35 (t, 2H, *J* 8.7 Hz, CH), 4.84 (d, 2H, *J* 5.4 Hz, CH), 6.99–7.25 (m, 20H, ArH); δ_C (300 MHz, DMSO): 41.2, 54.3, 75.4, 125.6, 126.8, 127.1, 127.6, 128.1, 144.4, 145.0; ν_{max} (KBr): 3451, 3061, 3026, 2930, 2880, 1601, 1496, 1454, 1297, 1053, 1007, 754, 696; HRMS (ESI, MeOH): $[M+Na]^+$ calcd for $C_{30}H_{28}O_2Na$: 443.19815, found: 443.19766; (+)-**15**: $[\alpha]_D^{20}$ +33 (*c* 0.5, $CHCl_3$, 95% ee); HPLC: t_R=12.2 (Chiracel OD-H, hexane–*i*-PrOH, 9:1, v/v); (−)-**15**: $[\alpha]_D^{20}$ −17.7 (*c* 0.23, CHCl3, 48% ee); HPLC: t_R=16.8 (Chiracel OD-H, hexane–*i*-PrOH, 9:1, v/v).

4.3. Esterification of *rac*-15

Preparation of the diastereomeric esters with (*R*)-*O*-methylatrolactic acid was carried out using DCC-DMAP procedure according to the literature.[14] Diol **15** (0.51 g, 1.2 mmol) was added in one portion to the solution of (*R*)-*O*-methylatrolactic acid (0.4 g, 2.2 mmol) and DCC (0.5 g, 2.4 mmol) in dichloromethane (10 mL), followed by the addition of DMAP (30 mg, 0.24 mmol). The turbid solution was stirred at room temperature for 5 days. After that time the reaction mixture was diluted with diethyl ether (saturated with water) and stirred for 15 min. The precipitated solid was filtered off and the solution was evaporated to gave the oily product. Monoesters **16a**, **16b** and bisesters **17a**, **17b** were isolated by column chromatography (SiO_2, AcOEt/hexane=1:3, v/v).

*4.3.1. Monoester **16a***

Crystallizing oil, R_f (AcOEt/hexane, 1:3) 0.29; $[\alpha]_D^{20}$ +21 (*c* 1.2, $CHCl_3$, 85% ee); δ_H (300 MHz, $CDCl_3$): 1.54 (s, 3H, CH_3), 1.88 (br s, 1H, OH), 2.71 (ddd, 1H, *J* 6.0, 9.0, 9.0 Hz, CH), 2.86 (ddd, 1H, *J* 6.0, 9.1, 9.1 Hz, CH), 3.00–3.06 (m, 1H, CH), 3.10–3.15 (m, 1H, CH), 3.17 (s, 3H, CH_3), 4.59 (d, 1H, *J* 6.0 Hz, CH–O), 5.88 (d, 1H, *J* 5.7 Hz, CH–O), 6.87–7.34 (m, 25H, ArH); δ_C (300 MHz, $CDCl_3$): 21.1, 41.8, 51.7, 51.9, 54.3, 76.4, 78.0, 81.4, 126.0, 126.1, 126.2, 126.4, 126.6, 127.3, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.1, 128.3, 137.5, 140.6, 141.8, 142.4, 142.5, 172.0; ν_{max} (film): 3487, 3086, 3062, 3029, 3004, 2987, 2935, 2856, 1739, 1603, 1496, 1455, 1247, 1138, 1115, 1074, 1050, 911, 759, 697, 548; HRMS (ESI, MeOH): $[M+Na]^+$ calcd for $C_{40}H_{38}O_4Na$: 605.2662, found: 605.2676.

*4.3.2. Bisester **17a***

White solid, mp 137–138.5 °C (toluene/hexane); R_f (AcOEt/hexane, 1:3) 0.41; $[\alpha]_D^{20}$ +10.3 (*c* 0.76, $CHCl_3$, 95% ee); δ_H (300 MHz, $CDCl_3$): 1.38 (s, 6H, CH_3), 2.80 (br s, 4H, CH), 3.08 (s, 6H, OCH_3),5.69 (d, 2H, *J* 2.7 Hz, CH–O), 6.78 (d, 4H, *J* 6.6 Hz, ArH), 6.93–7.27 (m, 26H, ArH); δ_C (300 MHz, $CDCl_3$): 20.7, 42.5, 51.7, 52.2, 78.2, 81.1, 126.2, 126.6, 127.4, 127.8, 127.9, 128.1, 128.2, 137.1, 140.3, 141.6, 171.7; ν_{max} (KBr): 3092, 3059, 3041, 3029, 2992, 2955, 2830, 1719, 1601, 1497, 1449, 1227, 1137, 1112, 944, 775, 753, 698, 551; HRMS (ESI, MeOH): $[M+Na]^+$ calcd for $C_{50}H_{48}O_6Na$: 767.3343, found: 767.3374.

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