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The synthesis of C_2 symmetry diesters of (3*R*,4*R*)-TTFOL through a green and stereoselective (2*R*,3*R*)-TADDOL rearrangement

Andrea R. Costantino [a], María Gabriela Montiel Schneider [a], Antonio Galdámez [b], Romina A. Ocampo [a], Sandra D. Mandolesi [a,*], Liliana C. Koll [a,*]

[a] Departamento de Química e INQUISUR (UNS/CONICET), Universidad Nacional del Sur, Avda. Alem 1253, Bahía Blanca 8000, Argentina
[b] Departamento de Química, Facultad de Ciencias, Universidad de Chile, Las Palmeras 3425, Ñuñoa, 7750000 Santiago, Chile

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ABSTRACT

An efficient, green, and atom economic methodology for the stereoselective synthesis of C_2 symmetry (3*R*,4*R*)-TTFOL diester derivatives has been developed. The procedure occurs through a (2*R*,3*R*)-TADDOL dioxolane cleavage and rearrangement under mild conditions by its reaction with a carboxylic acid in the presence of TFAA/H_3PO_4 without the need for an inert atmosphere to give generally high yields.

1. Introduction

Selective reaction on a functional group in a polyfunctional compound is very useful in organic synthesis and involves the use of specific protecting groups. Among them, ketal formation is most commonly used for the protection of 1,2- and 1,3-diols. There have also been many studies concerning its selective deprotection.[1] The cleavage of ketals by acid catalyzed hydrolysis or by oxidative conditions is particularly difficult if the substrate contains other labile groups.

The tartaric acid derivative, tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol **1** (TADDOL) and other C_2 symmetry analogous compounds can be easily synthesized and are also extraordinarily versatile chiral auxiliaries, which have found numerous and widespread applications as ligands in asymmetric transformations.[2] The TADDOL acetonide group is known to be rather stable, surviving many work-up procedures.[3] To the best of our knowledge, the ketal moiety is hydrolyzed only under high torsional strain conditions under which the dioxolane ring is significantly more labile to ring-opening reactions than is usually the case for TADDOLs.[4]

Herein we report an unusual case for diacetonide ring opening during TADDOL esterification in acid media with structural rearrangement, leading to the diesters of another known sterically hindered C_2 chiral diol, (3*R*,4*R*)-TTFOL, (2,2,5,5-tetraphenyltetrahydrofuran-3,4-diol) **6**.[5] This compound is a potential chiral auxiliary agent for asymmetric synthesis, including asymmetric aldol reactions catalyzed by (*S*)-proline[5b] and Michael additions.[6]

2. Results and discussion

As part of studies into the synthesis of macrodiolides through radical tandem cyclohydrostannations,[7] we prepared some unsaturated TADDOL diesters. Among the several tested methods, the simplest and most straightforward one is the esterification involving the reaction of unsaturated acid chlorides with TADDOL pretreated with *n*-butyllithium as shown in Scheme 1.[8]

Since *n*-BuLi solution is not always commercially easy to access (it has high additional cost due to shipping by sea), we searched for an alternative esterification procedure that would allow us to circumvent its use. While attempting to carry out the reactions with low environmental impact, we also looked for esterification procedures that avoided the preparation and manipulation of acid chlorides (usually moisture sensitive, unstable, toxic, tedious to prepare, and waste generators).

Given the excellent results obtained in our previous studies into the esterification of (*S*)-1,1′-binaphthyl-2,2′-diol (BINOL) with trifluoroacetic acid anhydride (TFAA)/H_3PO_4 under a normal open atmosphere,[9] and taking into account that the procedure is also applicable to aliphatic alcohols,[10] we decided to analyze the possibility of carrying out the TADDOL esterification through this methodology. This reaction proceeds with low environmental impact under mild conditions and involves the formation of a mixed acid anhydride.[11] The trifluoroacetic acid (TFA) formed as a by-product, possesses special advantages over most mineral

* Corresponding authors. Tel.: +54 0291 4595100; fax: +54 291 4595187.
E-mail addresses: sdmando@criba.edu.ar (S.D. Mandolesi), lckoll@criba.edu.ar (L.C. Koll).

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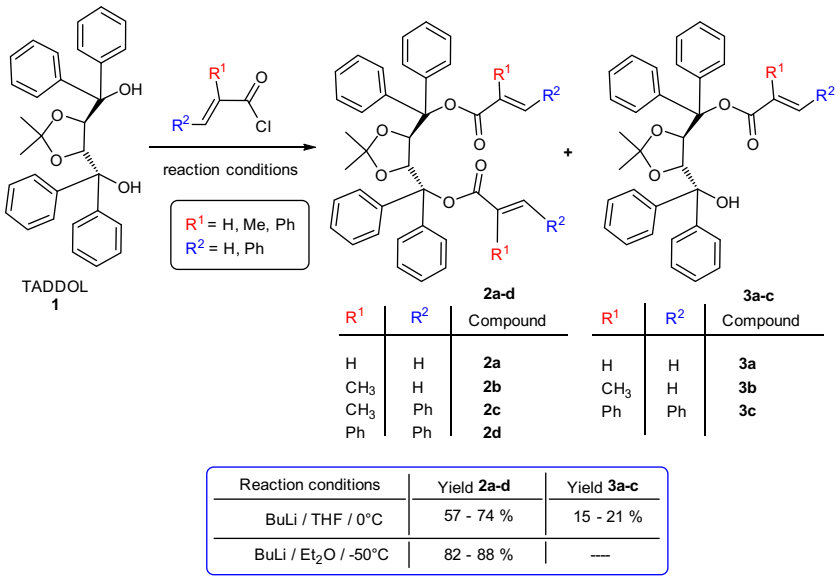


Reaction conditions	Yield **2a-d**	Yield **3a-c**
BuLi / THF / 0°C	57 - 74 %	15 - 21 %
BuLi / Et_2O / -50°C	82 - 88 %	----

Scheme 1. Esterification of (2*R*,3*R*)-TADDOL with acid chlorides and *n*-BuLi.

acids because of its low boiling point, so it can be readily and completely removed after completion of the reaction. Moreover, it can be recovered and reconverted into TFAA,[12] thus prompting us to consider this method as of low environmental impact and with high atomic economy.

Accordingly, we studied the esterification reaction of TADDOL **1** with acrylic acid in the presence of TFAA and H_3PO_4 as the catalyst at 50 °C under an air atmosphere. The reaction was carried out by mixing **1** with an excess of TFAA and catalytic H_3PO_4 in a vessel equipped with an open to air condenser, heating with stirring until TLC analysis indicated the disappearance of the substrate. Although trifluoroacetic acid can be used for the deprotection of dioxolanes,[13] we expected that TADDOL would be resistant to this acid, especially because of the mild reaction conditions employed and the intrinsically lower reactivity in the acetonide portion. However in our case, the situation was different. After work-up, the NMR spectra of the crude product showed the absence of the dioxolane moiety. The isolated product was established to be structure **4a** (Scheme 2, R^1,R^2 = H). We repeated the synthesis with different α,β-substituted derivatives of acrylic acid with similar results (products **4b**–**4g**, Scheme 2) and obtained high yields (85–93%) after 10 min of reaction at 50 °C. The products obtained were recrystallized in ethanol, except for **4f** and **4g** which were purified through column chromatography with Flash silica gel. These latter two products are caffeic acid derivatives similar to those used in the synthesis of HIV integrase inhibitors in virus replication,[14] where the conformational constraint of the five-membered heterocycle enhances the biological activity.[15]

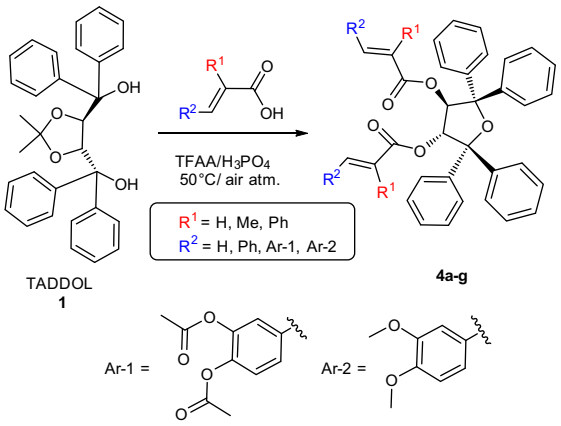
With the aim of extending the analysis of this unexpected transformation and determining which reaction step was involved in the dioxolane ring opening, we studied the reaction of diester **2a** with TFAA/H_3PO_4 and observed that under the same reaction conditions the diester remained unchanged.

Given these results, we propose the mechanism as shown in Scheme 3 in order to explain the generation of products **4a**–**4g**, which involves a bicyclic intermediate **5** (2,2-dimethyl-4,4,6,6-tetraphenyl tetrahydrofuro[3,4-*d*][1,3]dioxole). This highly strained *trans*-configured bicyclo-[3.3.0] skeleton, destabilizes the ketal moiety to such an extent that it breaks, leading to diol **6** [(3*R*,4*R*)-TTFOL], which could then be esterified by the mixed anhydrides leading to the di-esterified products **4a**–**g**. Seebach et al. have reported the formation of **6** as a by-product in the chlorination of TADDOL with CH_3SO_2Cl,[16] and a convenient synthetic procedure was reported by Shan et al.[5b]

Two mechanistic pathways seem to be probable in order to justify the formation of intermediate **5**, as indicated in Scheme 3. In path A, the protonation of one of the TADDOL hydroxyl groups is proposed, followed by water release to form a tertiary carbocation that cyclizes in an intramolecular way to give a tetrahydrofurane ring by means of the second hydroxyl group. In path B, TADDOL could react with TFAA to form a mono-trifluoroacetyl ester **7** which in turn is protonated and loses the TFA to form the tertiary carbocation that cyclizes to **5**.

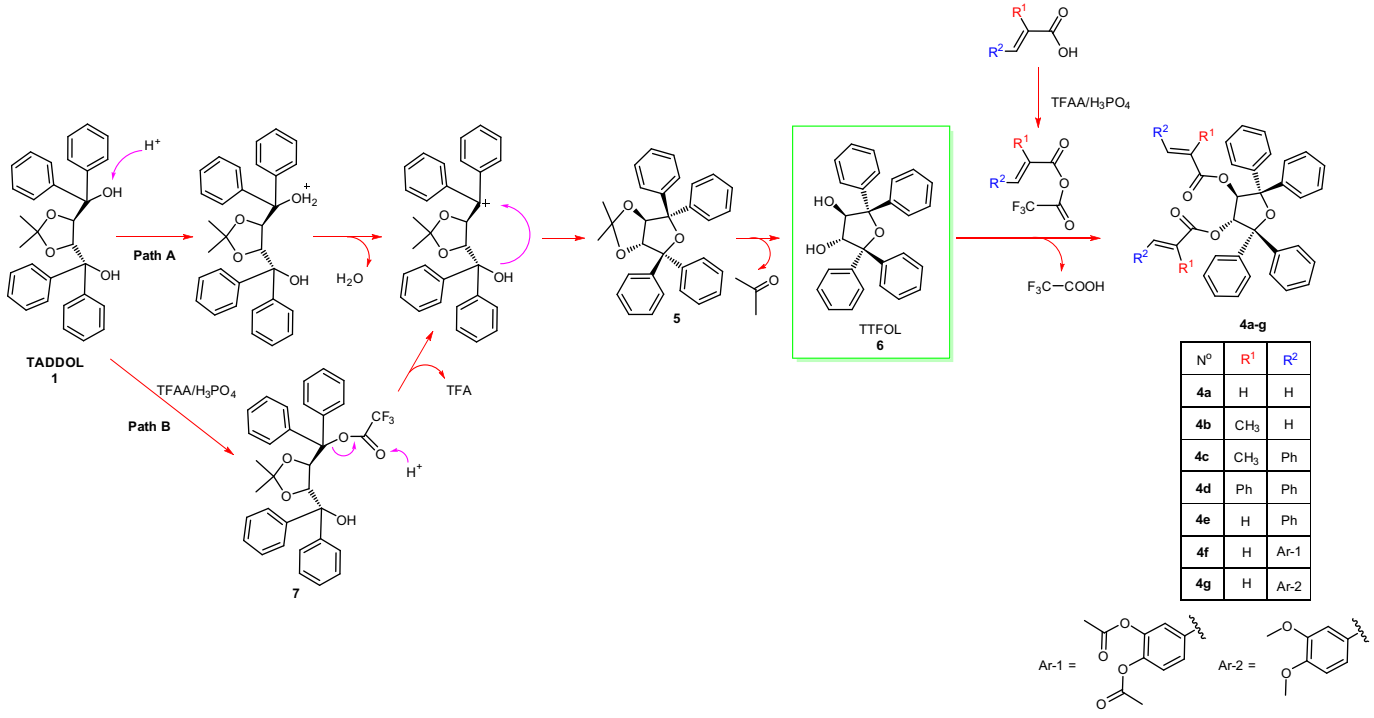
Unfortunately we were unable to isolate the reaction intermediates that would allow us to confirm the proposed mechanism. Therefore a dynamic NMR experiment was performed, dissolving in a NMR tube TADDOL, TFAA, and H_3PO_4 in $CDCl_3$. During the ^1H NMR experiment we observed the appearance of a peak at 2.34 ppm, attributed to the acetone release during the cleavage of the dioxolane ring from **5** to **6**, but no signal of water could be detected, thus suggesting that path B is the most probable way for the formation of bicycle **5**. Furthermore, we observed the disappearance of the quaternary carbon of the dioxolane TADDOL moiety at 109–110 ppm and the presence of acetone peaks (30.13 and 209.00 ppm) in the ^{13}C NMR spectra recorded during the experience. After this dynamic NMR analysis, a vacuum was applied to the solution in order to eliminate any volatile compounds (excess TFAA, TFA, and acetone released) and the residue was dissolved in $CDCl_3$ to acquire the ^1H, ^{13}C NMR, and ^{19}F NMR spectra. We observed two peaks at −75.06 and −75.66 ppm in the ^{19}F NMR spectrum that could be assigned to the mono- and bis-trifluoroacetyl esters of TTFOL, respectively, both apparently in the mixture. The ^1H NMR spectrum of this sample shows signs that could correspond to these compounds and TTFOL. Furthermore, the peaks at 77 and 84 ppm, observed in the previous dynamic ^{13}C NMR spectrum, may be attributed to C3 and C4 in the substituted furanose ring.

The structure of product **4b** was confirmed by X-ray crystallographic analysis. The skeleton of the molecule is depicted in Figures 1 and 2 with its atomic displacement ellipsoid plot and atom labels. The 5-membered furanose ring (O5/C9/C6/C7/C11) adopts a twisted conformation on C6–C7 atoms as indicated by



Compound	R^1	R^2	Yield (%)	$[\alpha]_D^{25}$
4a	H	H	93	-75.1 (*c* 0.010, $CHCl_3$)
4b	CH_3	H	91	-114.9 (*c* 0.009, $CHCl_3$)
4c	CH_3	Ph	89	-105.0 (*c* 0.011, $CHCl_3$)
4d	Ph	Ph	85	-99.5 (*c* 0.011, $CHCl_3$)
4e	H	Ph	93	+38.1 (*c* 0.010, $CHCl_3$)
4f	H	Ar-1	52	+45.5 (*c* 0.27, $CHCl_3$)
4g	H	Ar-2	28	+67.3 (*c* 0.011, $CHCl_3$)

Scheme 2. Synthesis of (3*R*,4*R*)-TTFOL diesters from TADDOL in $TFAA/H_3PO_4$.



Scheme 3. Proposed mechanism for the synthesis of TTFOL diesters **4a–g** from TADDOL in $TFAA/H_3PO_4$ with structural rearrangement.

the Cremer and Pople puckering parameters: Q2 is 0.373(2) Å and φ2 is 95.7(4)°.[17] The C9–O5 bond distance [1.446(3) Å] agrees well with the similar bonds in related compounds.[18] The torsion angle O4–C7–C6–O3, in **4b**, is −166.82(16)°. All relevant structural parameters (bond distances and angles) are as expected and in acceptable agreement with other organic molecules.[14] In the crystal of **4b**, molecules are linked by intermolecular C—H···O=C contacts and C—H···π intramolecular interactions forming a supramolecular network (Fig. 3). The carbonyl group forms a C24—H24···O1 [symmetry code: 1/2 + *x*, 1/2 − *y*, 1 − *z*] interaction

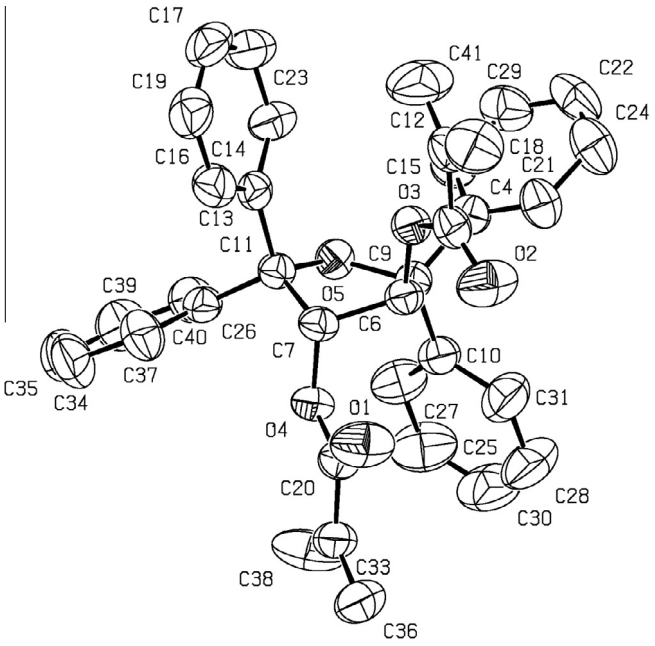


Figure 1. ORTEP diagram of **4b** showing the crystal structure.

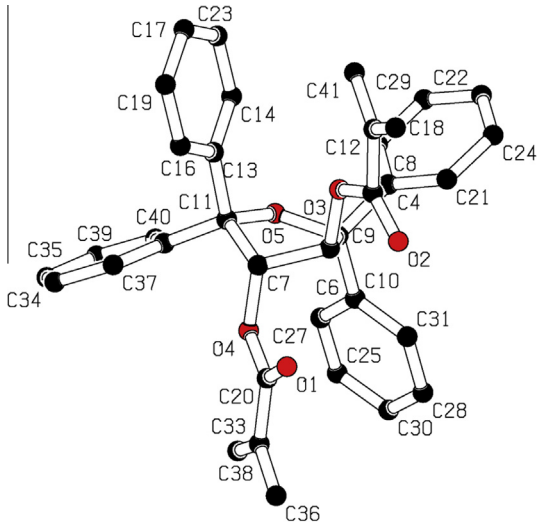


Figure 2. Structural representation of **4b** with atom label.

with a distance of 2.58 Å and an angle of 121.0°. These intermolecular interactions constitute chains with a graph-set descriptor C (10) motifs.[19] The network is reinforced by intramolecular C—H···π interactions.[20] H41B is oriented toward the face of an aromatic ring. The C41—H41B···*Cg* distance is 2.66 Å and angle of 174°. *Cg* is the centroid of the C13/C14/C16/C17/C19/C23 ring.

A bicyclic intermediate similar to **5** (with a tetrahydrothiophene ring) was previously detected by Haunschmidt et al.[21] through electrospray ionization high resolution mass spectrometry (ESI-HRMS) while monitoring the oxidation reaction with peracetic acid of bisthioacetate derived from TADDOL carried out at 0 °C. At room temperature, they could not detect the bicyclic intermediate, which is indicative of its high instability, attributed to a high angular deformation. Therefore, the driving force is the release of the strain energy.

Although it was not possible to isolate the bicyclic intermediate **5**, we believe that the formation of the rearranged product **6** should occur without racemization through such structure, leading to (3*R*,4*R*)-TTFOL diesters starting from (2*R*,3*R*)-TADDOL. The 3D arrangement of **4b** determined by X-ray analysis confirms the proposed configuration for the final product. The presence of the two pairs of germinal phenyl groups may favor the cyclization,[22] but is disfavored by the tightness of the bicyclo [3,3,0] octane system.

Through molecular mechanics calculations (**MMFF94**-Merck Molecular Force Field 94) we were able to determine that the dihedral angle (ϕ) of the O—C—C—O bond of TADDOL **1** (ϕ = 43°) and the C—C—C—C bond of TTFOL **6** (ϕ = 45°) were lower than they are in the bicyclic structure **5** (ϕ = 47° and 49°, respectively). Furthermore, the bridgehead carbons in **5** exhibit a significant angular deflection (124°), and the C—C bond between the bridgehead atoms is shorter in the bicyclic structure than the equivalent link in dioxolanes (see Scheme 4). The highly forced structure **5** seems to be responsible for the dioxolane cleavage.

3. Conclusion

The methodology presented herein illustrates the usefulness of TFAA/H_3PO_4 as an efficient agent for performing the TADDOL dioxolane cleavage and structural reorganization with configurational retention for the stereoselective synthesis of TTFOL diester derivatives by means of a mixed anhydride methodology. The highly strained *trans*-configured bicyclo [3.3.0] skeleton may be responsible for the sensitivity of the dioxolane ring, and therefore it is more labile to ring-opening reactions than normal TADDOLs.

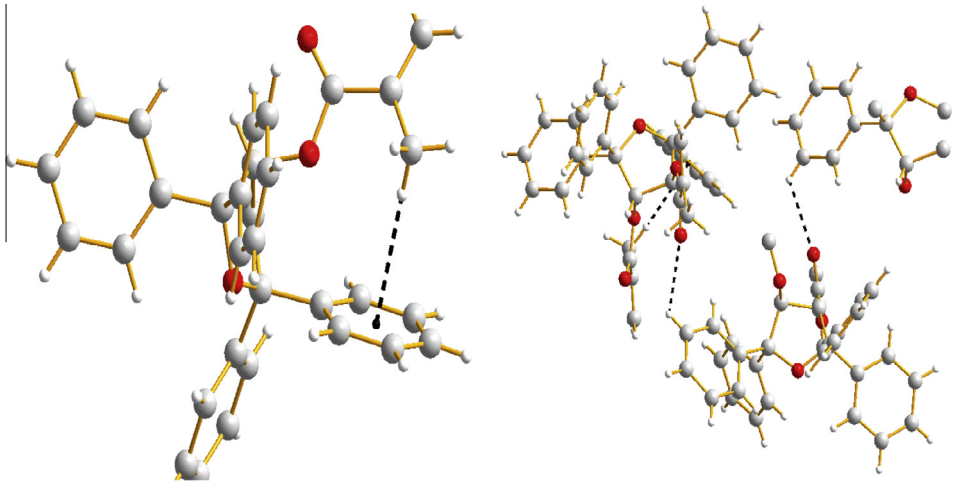
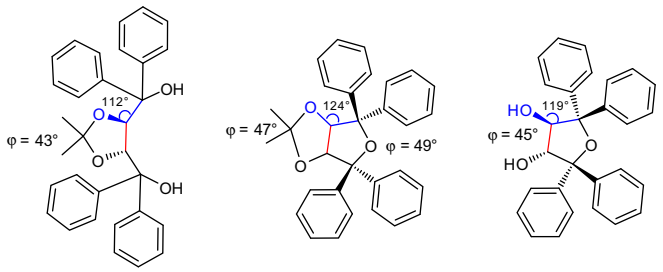


Figure 3. Structural representation of **4b** with DIAMOND program showing the intermolecular C—H···O=C contacts and C—H···π intramolecular interactions.



Scheme 4. Molecular mechanics calculations.

Due to the operational simplicity, mild reaction conditions and short reaction time this is a useful method for the synthesis of C_2 symmetry (3*R*,4*R*)-TTFOL-diester derivatives in good to excellent yields from commercially available (2*R*,3*R*)-TADDOL within a few minutes. Furthermore, the procedure does not require the use of expensive reagents or catalysts, or an inert or anhydrous atmosphere. Further studies are currently in progress with the aim of determining the scope and limitations of the procedure.

To the best of our knowledge, the TTFOL diesters **4a**–**g** are new, and so by using this methodology, we have synthesized and characterized seven new enantiomerically pure C_2 symmetry compounds with potential applications in enantioselective organic synthesis and also for biological uses.

4. Experimental

4.1. General

All commercially available chemicals and solvents were of analytical reagent grade and used without further purification. TADDOL was prepared as described in the literature.[23] Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using 5% phosphomolybdic acid in ethanol. Flash chromatography purifications were carried out using Aldrich silica gel 60 (230–400 mesh). NMR spectra were obtained using a Bruker ARX 300 instrument. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 300, 75.4 and 377 MHz, respectively. Chemical shifts (δ) are reported in ppm with respect to TMS ($SiMe_4$) or $CHCl_3$ (δ = 7.26) in ^{1}H NMR, to the central $CDCl_3$ resonance (δ = 77.0) in ^{13}C NMR and relative to 2,2,2-trifluoroacetophenone (δ_F = −71.8) for ^{19}F NMR spectra. Multiplicities are given as: s (singlet), d (doublet), dd (double doublet) and m (multiplet). The number of protons (*n*) for a given resonance is indicated by *n*H. Coupling constants are reported as *J* values in Hz. Infrared spectra were recorded with a FT-IR Nicolet Nexus 470/670/870 spectrophotometer. Mass spectra were obtained using a Finnigan MAT Incos 50 Galaxy System (DIP-MS). High resolution mass spectra were recorded on a Finnigan MAT 900 (HR-EI-MS). Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Specific rotations were measured with a Polar L-μP, IBZ Messtechnik instrument. Crystallographic analyses were performed with a Bruker CCD diffractometer at the University of Chile. All spectra of compounds **4a**–**g** are reported from isolated products.

4.2. General procedure for the synthesis of (3*R*,4*R*)-TTFOL-diesters through TFAA/H_3PO_4 procedure

At first, TFAA (4.1 g, 2.76 mL, 0.020 mol) was added at room temperature to a stirred mixture of 0.5 g (1.07 mmol) of TADDOL, the required carboxylic acid (2.36 mmol) and 0.046 g (0.027 mL, 0.47 mmol) of H_3PO_4 in a two mouth round bottom flask equipped with a reflux condenser and magnetic stirrer, under a normal open atmosphere. During the addition, the reaction mixture became warm and brown. The course of the reaction was monitored by TLC until the disappearance of the starting compounds. After heating at 50 °C for approximately 10 min.,[†] the reaction mixture was cooled (ice water) and cold water (4 mL) was added. It was then extracted with ethyl acetate (3 × 10 mL), and the organic layer was separated and washed with 10% NaOH (2 × 10 mL) and water (2 × 10 mL). The combined aqueous layers were extracted with a second portion of ethyl acetate (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified as indicated in each case. The workup procedure mentioned above allows the complete removal of TFA, TFAA, H_3PO_4, and any unreacted carboxylic acid.

4.2.1. (3*R*,4*R*)-2,2,5,5-Tetraphenyltetrahydrofuran-3,4-diyl-diacrylate 4a

Compound **4a** was obtained following the general procedure 4.2 using acrylic acid. The crude product was purified by recrystallization in ethanol to yield 0.53 g (0.99 mmol, 93%) of (3*R*,4*R*)-TTFOL-diacrylate as a light yellow solid. $[\alpha]_D^{25}$ = −75.1 (*c* 0.010, $CHCl_3$), mp: 146–148 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ (ppm) = 5.37–5.66 (6H, m, 2 × CH_2 and 2 × CH), 6.39 (2H, s, 2 × CH), 6.98–7.18 (8H, m, H-Ar), 7.19–7.27 (8H, m, H-Ar), 7.57–7.63 (4H, m, H-Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) = 78.77, 89.90, 126.31, 126.79, 126.92, 127.11, 127.14, 127.60, 128.13, 131.93, 142.68, 144.63, 164.23; ESI-HRMS calcd $[M+Na]^+$ 539.1829; found 539.1835. Elemental Anal. Calcd for $C_{34}H_{28}O_5$: C, 79.05; H, 5.46. Found: C, 79.06; H, 5.47.

4.2.2. (3*R*,4*R*)-2,2,5,5-Tetraphenyltetrahydrofuran-3,4-diyl-dimethacrylate 4b

Compound **4b** was obtained following the general procedure 4.2 using methacrylic acid. The crude product was purified by recrystallization in ethanol to yield 0.55 g (0.97 mmol, 91%) of (3*R*,4*R*)-TTFOL-dimethacrylate as a white solid. $[\alpha]_D^{25}$ = −114.9 (*c* 0.009, $CHCl_3$), mp: 128–130 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ (ppm) = 1.25 (6H, s, 2 × CH_3), 5.13 (4H, dd, $^2J_{(H-H)}$ = 1.6 Hz, 2 × CH_2), 6.42 (2H, s, 2 × CH), 6.94–7.16 (8H, m, H-Ar), 7.17–7.32 (8H, m, H-Ar), 7.60–7.67 (4H, m, H-Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) = 17.40, 79.29, 90.96, 126.24, 126.64, 126.67, 126.70, 126.90, 127.55, 128.11, 134.96, 142.79, 144.68, 165.63, 166.89; ESI-HRMS calcd $[M+Na]^+$ 567.2142; found 567.2160. Elemental Anal. Calcd for $C_{36}H_{32}O_5$: C, 79.39; H, 5.92. Found: C, 79.42; H, 5.94.

4.2.3. (3*R*,4*R*)-2,2,5,5-Tetraphenyltetrahydrofuran-3,4-diyl-(*E*)-2-methyl-3-phenyl-propenoate 4c

Compound **4c** was obtained following the general procedure 4.2 using (*E*)-2-methyl-3-phenylpropenoic acid. The crude product was purified by recrystallization in ethanol to yield 0,68 g (0.95 mmol, 89%) of (3*R*,4*R*)-TTFOL-diyl-2-methyl-3-phenyl-propenoate as a white solid. $[\alpha]_D^{25}$ = −105.0 (*c* 0.011, $CHCl_3$), mp: 158–160 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ (ppm) = 1.43 (6H, s, 2 × CH_3), 6.57 (2H, s, 2 × CH), 6.67 (2H, s, 2 × CH), 6.88–7.49 (26H, m, H-Ar), 7.70–7.73 (4H, m, H-Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) = 13.33, 79.56, 91.63, 126.47, 126.69, 126.83, 127.04, 127.10, 127.61, 128.14, 128.29, 129.64, 135.65, 139.87, 142.93, 144.74, 166.89; ESI-HRMS calcd $[M+Na]^+$ 719.2768; found

[†] The removal of TFA by distillation as the initial isolation step is appropriate for large scale preparations; for the scale of the typical reaction as carried here, the following extraction procedure was used.

719.2772. Elemental Anal. Calcd for $C_{48}H_{40}O_5$: C, 82.73; H, 5.79. Found: C, 82.75; H, 5.81.

4.2.4. (3*R*,4*R*)-2,2,5,5-Tetraphenyltetrahydrofuran-3,4-diyl-(*E*)-2,3-diphenylpropenoate 4d

Compound **4d** was obtained following the general procedure 4.2 using (*E*)-2,3-diphenyl-2-propenoic acid. The crude product was purified by recrystallization in ethanol to yield 0.76 g (0.91 mmol, 85%) of (3*R*,4*R*)-TTFOL-diyl-2,3-diphenylpropenoate as an orange solid. $[\alpha]_D^{25} = -99.5$ (*c* 0.011, $CHCl_3$), mp: 73–75 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ (ppm) = 6.57–6.66 (6H, m, 2 × CH and H-Ar), 6.71 (2H, s, 2 × CH), 6.95–7.33 (32H, m, H-Ar), 7.69 (4H, m, H-Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) = 79.71, 90.50, 126.71, 128.28, 127.49, 127.71, 127.91, 128.16, 128.48, 128.97, 129.68, 130.64, 131.05, 134.39, 135.18, 141.13, 142.63, 144.45, 165.91; ESI-HRMS calcd $[M+Na]^+$ 843.3081; found 843.3090. Elemental Anal. Calcd for $C_{58}H_{44}O_5$: C, 84.85; H, 5.40. Found: C, 84.86; H, 5.41.

4.2.5. (3*R*,4*R*)-2,2,5,5-Tetraphenyltetrahydrofuran-3,4-diyl-(*E*)-3-phenylpropenoate 4e

Compound **4e** was obtained following the general procedure 4.2 using (*E*)-3-phenyl-2-propenoic acid. The crude product was purified by recrystallization in ethanol to yield 0.68 g (0.99 mmol, 93%) of (3*R*,4*R*)-TTFOL-diyl-3-phenylpropenoate as an orange solid. $[\alpha]_D^{25} = +38.1$ (*c* 0.010, $CHCl_3$), mp: 109–111 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ (ppm) = 5.87 (2H, d, $^3J_{(H-H)}$ = 16.0 Hz, 2 × CH), 6.51 (2H, s, 2 × CH), 6.67 (2H, d, $^3J_{(H-H)}$ = 16.0 Hz, 2 × CH), 6.96–7.37(26H, m, H-Ar), 7.65–7.70 (4H, m, H-Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) = 79.00, 90.29, 117.03, 126.45, 126.82, 127.02, 127.15, 127.65, 128.15, 128.75, 130.37, 134.16, 142.83, 144.90, 145.61, 164.83; ESI-HRMS calcd $[M+Na]^+$ 691.2563; found 691.2601. Elemental Anal. Calcd for $C_{46}H_{36}O_5$: C, 82.61; H, 5.43. Found: C, 82.60; H, 5.42.

4.2.6. (3*R*,4*R*)-2,2,5,5-Tetraphenyltetrahydrofuran-3,4-diyl-(*E*)-3-(3,4-diacetoxyphenyl) propenoate 4f

Compound **4f** was obtained following the general procedure 4.2 using (*E*)-3-(3,4-diacetoxyphenyl)propenoic acid (Ac_2-caffeic acid). The crude product was purified by silica gel 60 flash chromatography eluting with hexane/AcOEt (60:40) to yield 0.50 g (0.56 mmol, 52%) of (3*R*,4*R*)-TTFOL-di-(Ac_2-caffeoylate) **4f** as a yellow solid. $[\alpha]_D^{25} = +45.5$ (*c* 0.27, $CHCl_3$), mp: 66–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.20 (6H, s, 2 × CH_3), 2.22 (6H, s, 2 × CH_3), 5.77 (2H, d, $^3J_{(H-H)}$ = 16.0 Hz, 2 × CH), 6.45 (2H, d, $^3J_{(H-H)}$ = 16.0 Hz, 2 × CH), 6.49 (2H, s, 2 × CH), 6.93–7.38 (22H, m, H-Ar), 7.62–7.74 (4H, m, H-Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) = 20.59, 20.62, 78.97, 90.67, 117.80, 122.73, 123.72, 126.37, 126.77, 127.68, 128.18, 132.93, 142.27, 142.65, 143.55, 144.83, 164.30, 167.91, 167.96; ESI-HRMS calcd $[M+H]^+$ 901.1285; found 901.1283. Elemental Anal. Calcd for $C_{54}H_{44}O_{13}$: C, 71.99; H, 4.92. Found: C, 71.98; H, 4.91.

4.2.7. (3*R*,4*R*)-2,2,5,5-Tetraphenyltetrahydrofuran-3,4-diyl-(*E*)-3-(3,4-dimethoxyphenyl) propenoate 4g

Compound **4g** was obtained following the general procedure 4.2 using (*E*)-3-(3,4-dimethoxy phenyl)propenoic acid. The crude product was purified by silica gel 60 flash chromatography eluting with hexane/AcOEt (70:30) to yield 0.24 g (0.30 mmol, 28%) of (3*R*,4*R*)-TTFOL-di-(MeO_2-caffeoylate) **4g** as a white solid. $[\alpha]_D^{25}$ = +67.3 (*c* 0.011, $CHCl_3$), mp: 110–112 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ (ppm) = 3.81 (6H, s, 2 × CH_3), 3.82 (6H, s, 2 × CH_3), 5.77 (2H, d, $^3J_{(H-H)}$ = 16.0 Hz, 2 × CH), 6.47–6.80 (6H, m, 4 × CH and 2 × H-Ar), 6.99–7.38 (20H, m, H-Ar), 7.61–7.71 (4H, m, H-Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) = 55.87, 55.97, 78.61, 89.81, 109.73, 110.91, 114.50, 122.79, 126.52, 127.10, 127.60, 128.14, 142.92, 145.01, 145.58, 149.08, 151.22, 165.01; ESI-HRMS calcd $[M+Na]^+$ 811.2877; found 811.2875. Elemental Anal. Calcd for $C_{50}H_{44}O_9$: C, 76.13; H, 5.62. Found: C, 76.12; H, 5.60.

4.3. Crystallographic data for (3*R*,4*R*)-TTFOL-dimethacrylate 4b

The diffraction experiment was performed for a 0.20 × 0.19 × 0.10 mm crystal. X-ray data were collected at 293 (2) K with a Bruker CCD diffractometer using MoKa radiation (0.71073).[24] The structure was solved in the orthorhombic P212121 (No. 19) space group with direct methods and refined with the full-matrix least-squares method on F^2 with the use of SHELX-97 program package (Sheldrick, 1997).[25] All H atoms were positioned geometrically and constrained to ride on their parent atoms. The absolute configuration was determined from the Flack parameter. The structural data have been deposited with Cambridge Crystallographic Data Centre, CCDC number 1058797.

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