Synthesis of Chiral 3-Substituted Phthalides via Rhodium(I)-catalyzed Crossed Alkyne Cyclotrimerisation

Bernhard Witulski,* Axel Zimmermann

Fachbereich Chemie, Universität Kaiserslautern, Erwin-Schrödinger-Straße, 67663 Kaiserslautern, Germany
Fax +49(631)2053921; E-mail: witulski@rhrk.uni-kl.de

Received 23 July 2002

Abstract: 3-Substituted phthalides were synthesized for the first time by crossed alkyne cyclotrimerisations with Wilkinson's catalyst. Esterification of propiolic acids with chiral propargylic alcohols by either the DCC/DMAP or the Mitsunobu method allows the synthesis of either enantiomeric form of diyne esters, that are used in crossed alkyne cyclotrimerisations with acetylene to provide 3-substituted phthalides in both enantiomeric forms.

Key words: phthalides, alkyne cyclotrimerisation, Wilkinson's catalyst, propargylic alcohols, (*S*)-3-*n*-butylphthalide

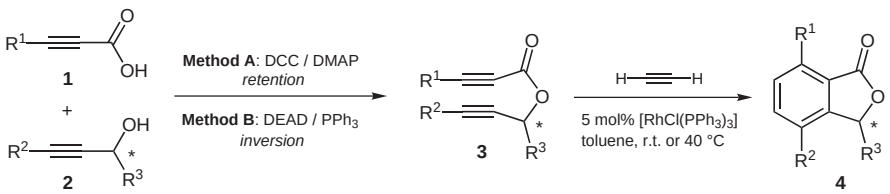
Considerable interest is devoted to the synthesis of 3-substituted phthalides [1(3*H*)-isobenzofuranones] comprising a large and diverse group of naturally occurring and biological active compounds.[1] For example, (*S*)-3-*n*-butylphthalide[2] is a constituent of the Chinese medical plant Dong Quai and of celery seed oil[3] and other 3-alkylphthalides form parts of several alkaloids with pharmaceutical relevance, such as noscapin, bicucullin and hydrastin.[4] Furthermore, phthalides bearing an aryl substituent at the 3-position are used as key intermediates for the synthesis of tri- and tetracyclic aromatic natural products, such as the anthracycline antibiotics.[5] Although a variety of methods for the preparation of phthalides has been reported[6] there are only a few reports on their synthesis by catalytic means.[7] Many of these start from already functionalised aromatic rings and focus on the formation of the δ-lactone moiety, whereas strategies relying on the construction of the aromatic core are rare.[8–10] For instance, phthalides obtained from transition metal promoted alkyne cyclotrimerisations have so far only been reported for a few simple cases using either a nickel(0) catalyst[9] or stoichiometric amounts of nickel(0) complexes.[10]

Herein we describe a flexible and efficient method for the assembly of substituted phathlides **4** that is based on two complementary ways for the formation of diyne esters **3** and their use in crossed alkyne cyclotrimerisations with acetylene applying Wilkinson's catalyst [$RhCl(PPh_3)_3$] (Scheme 1).

Since the pioneering work of Müller[11] and Grigg[12] in utilizing [$RhCl(PPh_3)_3$] for alkyne cyclotrimerisations, this protocol has been subsequently explored by others.[13] Crossed alkyne cyclotrimerisations with Wilkinson's catalyst serve well for the synthesis of indanes,[12] dihydroisobenzofuranes,[12] isoindolines,[12,13d] indolines,[13d] and carbazoles.[13g] However, the applicability of electron deficient diynes in a truly catalytic version of this method for the synthesis of phthalides has not been reported so far.

Propiolic acids **1** and propargylic alcohols **2** are readily accessible substrates,[14] and furthermore several methods for the preparation of optically active propargylic alcohols by asymmetric protocols are available.[15] We therefore thought that a strategy as outlined in Scheme 1 should not only serve for the synthesis of optically active 3-substituted phthalides but also allow their assembly with a high degree of structural diversity.

At the outset of our studies we investigated the DMAP-catalyzed (5 mol%) ester formation between propiolic acids **1** and propargylic alcohols **2** in the presence of dicyclohexyl carbodiimide (DCC).[16] Optimal yields of diyne esters **3** were obtained when a twofold excess of either **1** or **2** was used. The reactions were carried out in CH_2Cl_2 at –78 °C and then brought to room temperature over a period of several hours (8–10 h). The products **3a–i** could be purified by column chromatography on silica gel using hexanes/diethyl ether and were obtained in yields ranging from 42–84% (Method A, Table 1).[17]

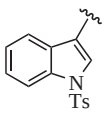
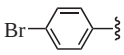
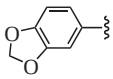
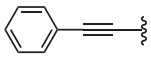


Scheme 1 Synthesis of substituted phthalides **4** via crossed alkyne cyclotrimerisations with Wilkinson's catalyst

Synlett 2002, No. 11, Print: 29 10 2002.
Art Id.1437-2096,E;2002,0,11,1855,1859,ftx,en;G20402ST.pdf.

ISSN 0936-5214

Table 1 Formation of Diyne Esters **3** via Method A (DCC/DMAP) and Method B (Mitsunobu Reaction)[17]

Entry	**1**	R^1	**2**	R^2	R^3	**3**	Method	Yield (%)[a]
1	**1a**	H	**2a**		H	**3a**	A B	84 81
2	**1b**		**2b**	H	H	**3b**	A B	83 89
3	**1a**	H	**2c**	H		**3c**	A B	60 65
4	**1a**	H	**2d**	H		**3d**	A B	60 65
5	**1a**	H	**2e**	H		**3e**	A B	60 75
6[b]	**1a**	H	**2f**	H		**3f**	A B	56 18
7	**1a**	H	(*S*)-**2g**	H		(*S*)-**3g**	A	59
8	**1a**	H	(*S*)-**2h**	H	CH_3	(*S*)-**3h** (*R*)-**3h**	A B	42 46
9	**1b**		(*S*)-**2h**	H	CH_3	(*S*)-**3i** (*R*)-**3i**	A B	79 71

[a] Isolated yields after column chromatography on silica gel.
[b] A 1:1 mixture of *E*/*Z*-isomers of the propargylic alcohol **2f** was used.

Alternatively, **1** and **2** were coupled to form esters **3** by the Mitsunobu reaction (Method B, Table 1). Addition of PPh_3 (2.8 mmol) to a THF solution containing alcohol **2** (1.4 mmol), propiolic acid **1** (2.1 mmol) and DEAD (2.8 mmol) at room temperature gave **3a**–**i** in yields of the same order of magnitude as method A, with the exception of allylic alcohol **2f** (entry 6). Since ester formations under DCC conditions proceeded with complete retention, and those by the Mitsunobu reaction with complete inversion,[18] both methods complemented each other perfectly allowing the synthesis of either enantiomer of the esters **3h** or **3i** starting from (*S*)-**2h**.[19]

Gratifyingly, the electron deficient diyne esters **3a**–**i** underwent crossed alkyne cyclotrimerisations with acetylene efficiently to give the substituted phthalides **4** in good to excellent yields (Table 2).[20] Best results were obtained when the reactions were carried out in toluene (0.03 M solution of **3**) under 1 atm of acetylene and in the presence of 5 mol% Wilkinson's catalyst. Crossed alkyne cyclotrimerisations with the terminal diynes **3c**–**h** and acetylene (1 atm) proceeded readily at room temperature, whereas the monosubstituted diyne esters **3a**, **3b** and **3i** needed smooth heating to 40 °C for completion of the reaction.

All reactions showed good chemoselectivity with no homo cyclotrimerisation of **3**. It is noteworthy to mention, that neither an arylbromide (entry 3) nor an olefin functionality (entry 5) disturbed the overall efficiency of the catalytic process. The method served well for the synthesis of phthalides having an aryl substituent at the 3-position. Following this protocol the optically active phthalides **4f**–**h** were obtained in good yields without any detectable racemisation (Table 2, entries 6–10). For example, the valuable natural product (*S*)-3-*n*-butylphthalide [(*S*)-**4f**, Table 2, entry 6] was obtained in 79% yield (88% ee) after cyclotrimerisation of (*S*)-**3g** (88% ee)[14] with acetylene at room temperature. Furthermore, both enantiomeric forms of **4g** were obtained with better than 94% ee (68% yield) starting either from (*S*)-**3h** or (*R*)-**3h**, whereas the latter was obtained by esterification with complete inversion of the configuration of (*S*)-**2h** (94% ee) after the Mitsunobu reaction.

Finally, we investigated the chemoselective outcome of the reaction of triyne **3e** with acetylene in the presence of 10 mol% of Wilkinson's catalyst at room temperature (Scheme 2). Products **5a** and **5b** were obtained in 54% yield and the observed product ratio (**5a**:**5b** = 6:1) indicates that crossed alkyne cyclotrimerisations preferentially involve terminal alkyne moieties.

In conclusion, crossed alkyne cyclotrimerisations with the electron deficient diyne esters **3** mediated by Wilkinson's catalyst offer a flexible and efficient access to chiral 3-substituted phthalides. The diyne esters themselves are readily available by either esterification following the Mitsunobu or the DCC/DMAP protocol allowing the synthesis of 3-substituted phthalides in either enantiomeric form starting from one configuration of the same chiral propargylic alcohol. Further investigations towards the extension of this methodology to the synthesis of natural

products and drug related targets as well as applications of this strategy to other heterocycles are underway in our laboratories.

Table 2 Crossed Alkyne Cyclotrimerisations of Diynes **3** with Acetylene (1 atm) in Toluene Catalyzed by 5 mol% [$RhCl(PPh_3)_3$] to Give Substituted Phthalides **4**[20]

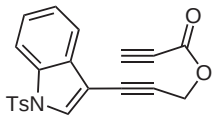
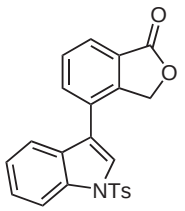
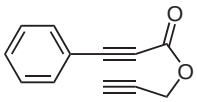
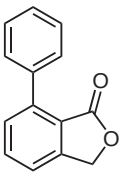
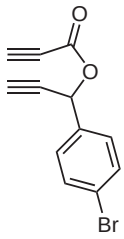
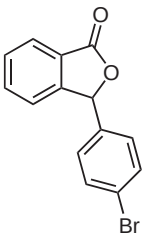
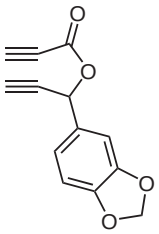
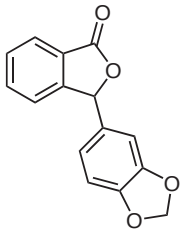
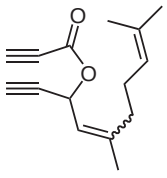
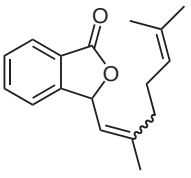
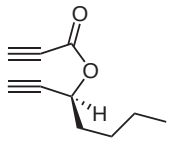
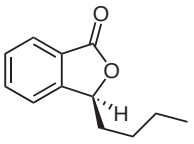
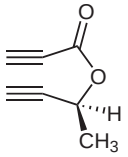
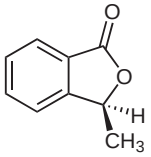
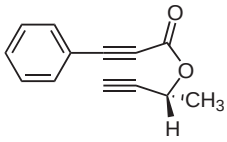
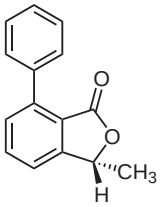
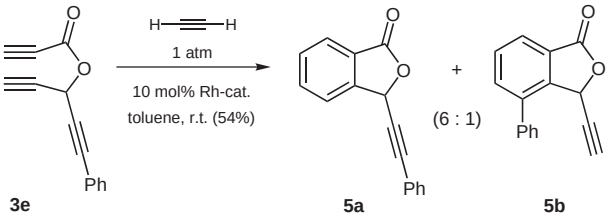
Entry	Diyne **3**	T (°C)[a]	Phthalide **4**	Yield (%)[b]
1	 **3a**	40	 **4a**	51
2	 **3b**	40	 **4b**	86
3	 **3c**	20	 **4c**	98
4	 **3d**	20	 **4d**	86
5	 **3f**	20	 **4e**	79
6	 (*S*)-**3g**	20	 (*S*)-**4f**	79

Table 2 Crossed Alkyne Cyclotrimerisations of Diynes **3** with Acetylene (1 atm) in Toluene Catalyzed by 5 mol% [$RhCl(PPh_3)_3$] to Give Substituted Phthalides **4**[20] (continued)

Entry	Diyne **3**	T (°C)[a]	Phthalide **4**	Yield (%)[b]
7	 (*S*)-**3h**	20	 (*S*)-**4g**	68
8	(*R*)-**3h**	20	(*R*)-**4g**	68
9	 (*R*)-**3i**	40	 (*R*)-**4h**	89
10	(*S*)-**3i**	40	(*S*)-**4h**	88

[a] Reaction times were not optimized and vary between 2–15 h.
[b] Isolated yields after column chromatography on silica gel.



3e **5a** **5b**

Scheme 2 Selectivity of the crossed alkyne cyclotrimerisations of **3e** with acetylene

Acknowledgement

Financial support of this work by the Fonds der Chemischen Industrie is gratefully acknowledged.

References

(1) (a) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*, Vol. 1; Academic Press: New York, **1975**, 249–264. (b) Barry, R. D. *Chem. Rev.* **1964**, *64*, 229.
(2) Several pharmacological effects ranging from anti-tumor, anti-asthmatic, anti-convulsant, anesthesia prolongation, $PGF_{2\alpha}$ inhibition, and cerebral anti-ischemic action have been attributed to 3-*n*-butylphthalides, see for example: (a) Zheng, G. Q.; Zhang, J.; Kenney, P. M.; Lam, L. K. T. *ACS Symp. Ser.* **1994**, *546*, 230. (b) Zheng, G. Q.; Kenney, P. M.; Zhang, J.; Lam, L. K. *Nutr. Cancer* **1993**, *19*, 77. (c) Liu, Z.; Song, Y.; Wang, W.; Chen, W.; Wang, X. *Zhongcaoyao* **1982**, *13*, 17. (d) Yu, S.; You, S.; Chen, H. *Yaoxue Xuebao* **1984**, *19*, 486; *Chem. Abstr.* **1984**, *101*, 222490c. (e) Sato, H.; Yorozu, H.; Yamaoka, S. *Biomed. Res.* **1993**, *14*, 385. (f) Ogawa, Y.; Hosaka, K.; Kubota, K.; Chin, M. JP 0477480, **1992**; *Chem Abstr.* **1992**, *117*, 69721n. (g) Wang, X. W. *Drugs Future* **2000**, *25*, 16.

(3) (a) Tang, W.; Eisenbrand, G. *Chinese Drugs of Plant Origin, Chemistry, Pharmacology, and Use in Traditional and Modern Medicine*; Springer-Verlag: Berlin, Heidelberg, **1992**. (b) Barton, D. H. R.; de Vries, J. X. *J. Chem. Soc.* **1963**, 1916. (c) Bjeldanes, L. F.; Kim, I.-S. *J. Org. Chem.* **1977**, *42*, 2333. (d) Bartschat, D.; Beck, T.; Mosandl, A. *J. Agric. Food. Chem.* **1997**, *45*, 4554.

(4) (a) Ke, Y.; Ye, K.; Grossniklaus, H. E.; Archer, D. R.; Joshi, H. C.; Kapp, J. A. *Cancer Immunol. Immunother.* **2000**, *49*, 217. (b) Ye, K.; Ke, Y.; Keshava, N.; Shanks, J.; Kapp, J. A.; Tekmal, R. R.; Petros, J.; Joshi, H. C. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 1601. (c) Mehta, A. K.; Ticku, M. K. *Brain Res. Rev.* **1999**, *29*, 196. (d) Kardos, J.; Blandl, T.; Luyen, N. D.; Doernyei, G.; Gács-Baitz, E.; Simonyi, M.; Cash, D. J.; Blaskó, G.; Szántay, C. *Eur. J. Med. Chem.* **1996**, *31*, 761. (e) Prager, R. H.; Tippett, J. M.; Ward, A. D. *Aust. J. Chem.* **1981**, *34*, 1085. (f) Hung, T. V.; Mooney, B. A.; Prager, R. H.; Tippett, J. M. *Aust. J. Chem.* **1981**, *34*, 383.

(5) (a) Sartori, G.; Bigi, F.; Tao, X.; Porta, C.; Maggi, R.; Predieri, G.; Lanfranchi, M.; Pellinghelli, M. A. *J. Org. Chem.* **1995**, *60*, 6588. (b) Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378. (c) Katsuura, K.; Snieckus, V. *Can. J. Chem.* **1987**, *65*, 124. (d) Katsuura, K.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 9. (e) Uemura, M.; Take, K.; Isobe, K.; Minami, T.; Hayashi, Y. *Tetrahedron* **1985**, *41*, 5771. (f) Uemura, M.; Take, K.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 858. (g) Broadhurst, M. J.; Hassall, C. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2227. (h) Snieckus, V. *Heterocycles* **1980**, *14*, 1649. (i) Kim, K. S.; Spatz, M. W.; Johnson, F. *Tetrahedron Lett.* **1979**, *20*, 331.

(6) Aryllithium reagents: (a) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Chem. Pharm. Bull.* **1991**, *39*, 3136. (b) Alexakis, A.; Sedrani, R.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 283. (c) Ogawa, Y.; Hosaka, K.; Chin, M.; Mitsuhashi, H. *Heterocycles* **1989**, *29*, 865. (d) Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; Baker, R. J. *Tetrahedron* **1983**, *39*, 1991. (e) Asami, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 17. (f) Dialkyl- and arylzinc reagents: Ogawa, Y.; Saiga, A.; Mori, M.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2000**, *65*, 1031. (g) See also: Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391. (h) See further: Soai, K.; Hori, H.; Kawahara, M. *Tetrahedron: Asymmetry* **1991**, *2*, 253. (i) See also: Watanabe, M.; Hashimoto, N.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1992**, *57*, 742. (j) Organotitanium reagents: Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Synthesis* **1992**, 681. (k) Another example: Olivero, A. G.; Weidmann, B.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 2485. (l) Borane reagents: Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205.

(7) BINAP-Ru(II) hydrogenation: (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509. (c) Transfer hydrogenation: Everaere, K.; Scheffler, J.-L.; Mortreux, A.; Carpentier, J.-F. *Tetrahedron Lett.* **2001**, *42*, 1899. (d) Ni-catalyzed cross couplings: Lei, J.-G.; Hong, R.; Yuan, S.-G.; Lin, G.-Q. *Synlett* **2002**, 927. (e) Bioreduction: Kitayama, T. *Tetrahedron: Asymmetry* **1997**, *8*, 253.

(8) (a) Padwa, A.; Weingarten, M. D. *J. Org. Chem.* **2000**, *65*, 3722. (b) Harland, P. A.; Hodge, P. *Synthesis* **1982**, 223. (c) Becher, J.; Nielsen, H. C.; Jacobsen, J. P.; Simonsen, O.; Clausen, H. *J. Org. Chem.* **1988**, *53*, 1862.

(9) Sato, Y.; Ohashi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5231.

(10) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2163.

(11) Müller, E. *Synthesis* **1974**, 761.

(12) (a) Grigg, R.; Scott, R.; Stevenson, P. *Tetrahedron Lett.* **1982**, *23*, 2691. (b) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357. (c) Grigg, R.; Sridharan, V.; Wang, J.; Xu, J. *Tetrahedron* **2000**, *56*, 8967.

(13) (a) Magnus, P.; Witty, D.; Stamford, A. *Tetrahedron Lett.* **1993**, *34*, 23. (b) McDonald, F. E.; Zhu, H. Y. H.; Holmquist, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 6605. (c) Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 2426. (d) Witulski, B.; Stengel, T.; Fernández-Hernández, J. M. *Chem. Commun.* **2000**, 1965. (e) Kotha, S.; Mohanraja, K. *Chem. Commun.* **2000**, 1909. (f) McDonald, F. E.; Smolentsev, V. *Org. Lett.* **2002**, *4*, 745. (g) Witulski, B.; Alayrac, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3281.

(14) (a) Propargylic alcohol (*S*)-**2h** (94% ee) is commercially available. The product, (*S*)-**2g** was obtained with 88% ee after (*S*)-alpine borane reduction of the corresponding ketone as described in the literature: Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851. (b) For the synthesis of (+)-propargylic alcohols via addition of lithium acetylide to aldehydes, see: Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.

(15) For recent achievements in the synthesis of optical active propargylic alcohols, see: (a) Franz, D. E.; Tomooka, C. S.; Fässler, R.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. (b) Schubert, T.; Hummel, W.; Müller, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 634.

(16) (a) Birtwistle, D. H.; Brown, J. M.; Foxton, M. W. *Tetrahedron* **1988**, *44*, 7309. (b) Maier, S.; Kazmaier, U. *Eur. J. Org. Chem.* **2000**, 1241.

(17) Selected data for diyne esters **3**:
3a: Mp: 101–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 1 H), 7.79–7.74 (m, 3 H), 7.64–7.59 (m, 1 H), 7.40–7.20 (m, 4 H), 5.06 (s, 2 H), 2.97 (s, 1 H), 2.33 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 145.4, 134.7, 134.0, 130.5, 130.0, 129.9, 126.9, 125.5, 123.8, 120.4, 113.5, 103.7, 85.9, 78.9, 75.9, 73.9, 54.4, 21.5. MS (EI): *m/z* (%) = 377 (100) [M^+]. Anal. Calcd for $C_{21}H_{15}NO_4S$: C, 66.83; H, 4.01; N, 3.71. Found: C, 66.99; H, 3.99; N, 3.60.
(*S*)-**3g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40 (dt, *J* = 6.7 Hz, *J* = 2.2 Hz, 1 H), 2.93 (s, 1 H), 2.52 (d, *J* = 2.2 Hz, 1 H), 1.87–1.81 (m, 2 H), 1.49–1.26 (m, 4 H), 0.93 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.6, 80.0, 75.4, 74.6, 74.3, 65.9, 34.1, 26.9, 22.1, 13.8. MS (EI): *m/z* (%) = 164 (8) [M^+].
(*S*)-**3i**: Mp: 59–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.58 (m, 2 H), 7.48–7.43 (m, 1 H), 7.40–7. 35 (m, 2 H), 5.56 (dq, *J* = 6.6, *J* = 2.2 Hz, 1 H), 2.53 (d, *J* = 2.2 Hz, 1 H), 1.60 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 133.0, 130.8, 128.6, 119.4, 87.1, 81.2, 80.2, 73.8, 61.7, 21.1. MS (EI): *m/z* (%) = 198(7) [M^+]. Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.82; H, 4.98.

(18) For reviews on the Mitsunobu reaction, see: (a) Dodge, J. A.; Nissen, J. S.; Presnell, M. *Org. Synth.* **1996**, *73*, 110. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (d) Castro, B. R. *Org. React.* **1983**, *29*, 1. (e) Mitsunobu, O. *Synthesis* **1981**, 1.

(19) The enantiopurity of the esters **3g–i** was analyzed after their conversion to the phthalides **4f–h,** that proceeded without any detectable racemisation.

(20) Selected data for phthalides **4**:
(*S*)-**4f**: Oil; $[\alpha]_D^{22}$ = –42 (*c* 0.45, $CHCl_3$); 88% ee as

determined by chiral capillary GLC analysis with Supleco Beta-Dex^{TM} 325; {lit.[6l] $[\alpha]_D^{22}$ –62 (*c* 0.42, $CHCl_3$)}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.6 Hz, 1 H), 7.67 (dt, *J* = 7.6 Hz, *J* = 3.3 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 5.49 (dd, *J* = 7.9 Hz, *J* = 4.1 Hz, 1 H), 2.10–2.01 (m, 1 H), 1.81–1.71 (m, 1 H), 1.53–1.33 (m, 4 H), 0.88 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 150.0, 133.8, 128.9, 126.0, 125.5, 121.7, 81.3, 34.3, 26.7, 22.3, 13.7. MS (EI): *m/z* (%) = 190(5) [M^+]. (*S*)-**4g**: oil; $[\alpha]_D^{22}$ = –22.1 (*c* 0.83, MeOH); 94% ee as determined by chiral capillary GLC analysis with Supleco Beta-Dex^{TM} 325. (*R*)-**4g**: $[\alpha]_D^{22}$ = +21.4 (*c* 0.81, MeOH); 94% ee as determined by chiral capillary GLC analysis with Supleco Beta-Dex^{TM} 325.
(*S*)-**4h**: $[\alpha]_D^{22}$ = –15.6 (*c* 0.94, $CHCl_3$). (*R*)-**4h**: $[\alpha]_D^{22}$ = +14.9 (*c* 0.98, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (t, *J* = 7.6 Hz, 1 H), 7.58–7. 55 (m, 2 H), 7.50–7.41 (m, 5 H), 5.56 (q, *J* = 6.6 Hz, 1 H), 1.69 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 152.5, 142.7, 136.4, 133.8, 130.8, 129.5, 128.3, 127.9, 121.8, 120.3, 76.1, 20.6. MS (EI): *m/z* (%) = 224(100) [M^+].