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Dehydrative Alkylation of Alcohols with Triethyl Methanetricarboxylate under Mitsunobu Conditions

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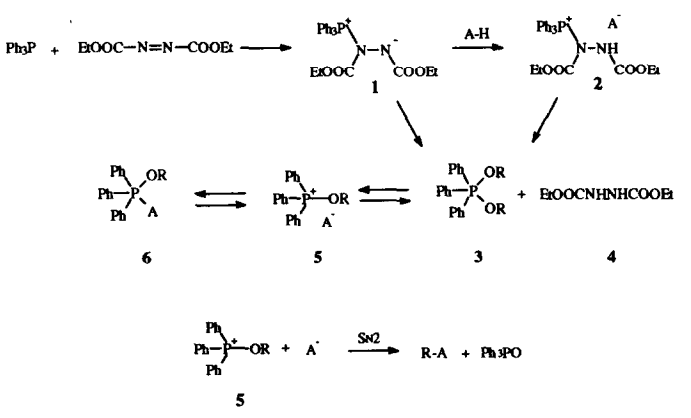
Abstract: Triethyl methanetricarboxylate (TEMT) can be mildly alkylated by primary, benzylic and allylic alcohols under classical Mitsunobu conditions, in fair to good yields. The utility of TEMT in organic synthesis as a diethyl malonate surrogate is reported.

In recent years there have been numerous reports on the application of the triphenylphosphine (TPP) - diethyl azodicarboxylate (DEAD) protocol [known as the Mitsunobu reaction (MR)[1]] in dehydrative bond-forming reaction (Eq. 1) over the past few years has been the subject of numerous reports.[2]

$$\text{R-OH} \xrightarrow[\text{TPP/DEAD}]{\text{A-H}} \text{R-A} \qquad \text{A = O-, N-, S-, C- nucleophiles} \qquad \text{Eq. 1}$$

In the presence of a suitable proton donor AH (*vide infra*) the alcohol ROH reacts with TPP-DEAD, to give reactive intermediate(s) which is(are) displaced by the conjugate base A^-, resulting in RA formation. Indeed, a careful scrutiny of the mechanism has indicated that, under certain conditions, cationic intermediates (*e.g.*, alkoxyphosphonium salts **5**) are present in equilibrium with neutral pentacoordinated species (*e.g.*, **3** and/or **6**, Scheme 1).

Scheme 1



The position of this equilibrium is heavily dependent on a) the steric size of substituent R; b) the nature of

the proton donor AH; c) the pK_{AH} value, and d) the polarity of the solvent.[3] In spite of the fact that C-O and C-N bond formations have wide applications, the most appealing C-C formation, under these mild and neutral conditions, is poorly documented.[2] Indeed, several experiments suggest a pK_{AH} threshold (*ca.* 11) above which AH is not deprotonated to a sufficient extent for efficient MR.[2c,4] The lack of carbon acids with an appropriate pK_{AH} value may partly explain the paucity of examples of C-C formation under Mitsunobu conditions. For example, diethyl malonate has a very low pK_{AH} value (13.3), and this has precluded any successful application of this protonated nucleophile.[5] Furthermore, MRs involving either 1,3-diketones or β-ketoesters resulted in the predominant formation of *O*-alkylated, rather than *C*-alkylated compounds.[2] To the best of our knowledge, except for the use of HCN derivatives,[6] and the above mentioned 1,3-dicarbonyl compounds, only *o*-nitroarylacetonitriles,[3e] γ-nitroalkanols[7] and some sulphones[8] appear to have been successfully tested. While exploring structural variants which may extend the range of applicability of MR, we found that triethyl methanetricarboxylate (TEMT) **7**,[9] a commercially available compound, acts as an expedient protonated C-nucleophile.

In this paper we report that TEMT can be alkylated by a wide array of alcohols under classical Mitsunobu conditions (Eq. 2), thus opening up interesting opportunities for preparative organic chemistry.

$$\underset{\mathbf{7}}{\text{H-C(COOEt)}_3} \xrightarrow[\text{TPP/DEAD}]{\text{ROH}} \text{R-C(COOEt)}_3 \qquad \text{Eq. 2}$$

r.t.

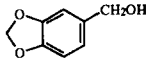
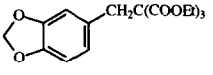
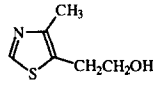
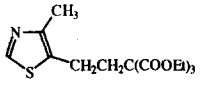
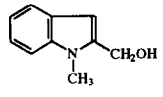
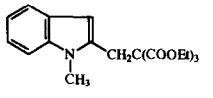
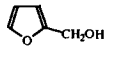
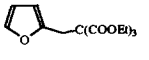
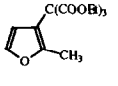
RESULTS AND DISCUSSION

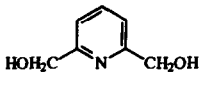
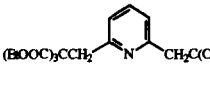
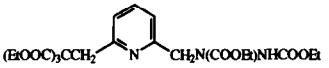
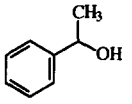
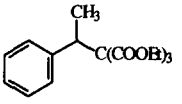
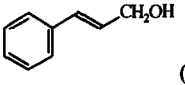
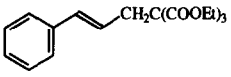
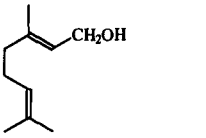
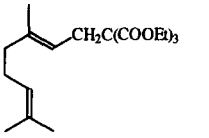
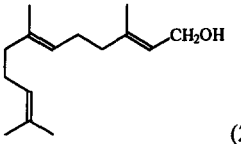
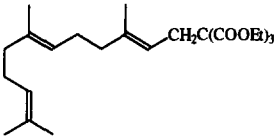
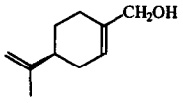
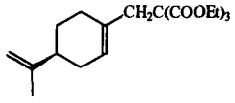
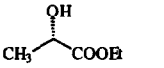
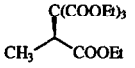
By virtue of the conjugate base low pK_{AH} (7.5)[10] value and good S_N2 behaviour, TEMT meets all the requirements for an efficient MR proton donor. Furthermore, the embodied $C(COOEt)_3$ group provides a handle for further synthetic manipulations, including the preparation of dendrimers,[11] malonates,[12] two-carbon elongated acids, α-alkylated allylic alcohols[13] and nitrogen containing heterocycles.[14]

Apart from the publication of a review article on the use of TEMT in organic synthesis,[9] we are not aware of any reported instance of alkylation under Mitsunobu conditions. Thus, to investigate the scope and limitation of this alkylation procedure, we selected a number of alcohols with different S_N2 reactivity. We found that primary, allylic and benzylic alcohols coupled smoothly with TEMT in Et_2O (unless stated otherwise) to give the respective alkylated compounds. In a typical reaction, a 0.6M solution of DEAD (1.5 equiv.) was added dropwise to an ice-cold solution containing the alcohol (1.0 equiv.), TPP (1.5 equiv.) and TEMT (1.2 equiv.) in Et_2O and an exothermic reaction took place (procedure A). The reaction was left to stir at r.t. until the alcohol was no longer present, as checked by TLC or GLC. During this time a white solid (TPP-oxide and diethyl hydrazinedicarboxylate **4**) precipitated from the reaction mixture. Any excess TEMT was easily removed by extraction with 5% Na_2CO_3 solution, thus facilitating the work-up procedure. Products were

recovered (after further purification, if necessary) in fair to good yields. For α-branched primary alcohols and secondary benzylic alcohols, the best results were generally obtained when the molar ratios for ROH:TEMT:TPP:DEAD were 1:1.5:2:2 (procedure B). Close examination of these reactions under various conditions including a) changing the solvent to THF or acetonitrile, b) using alternative redox systems,[15] c) higher temperatures (up to reflux), and d) altering the order of reagent addition did not significantly improve the isolated yields. As can be seen from Table 1, the reaction works equally well with unbranched primary, allylic and benzylic alcohols, and takes place in less than 30 min.

Table 1

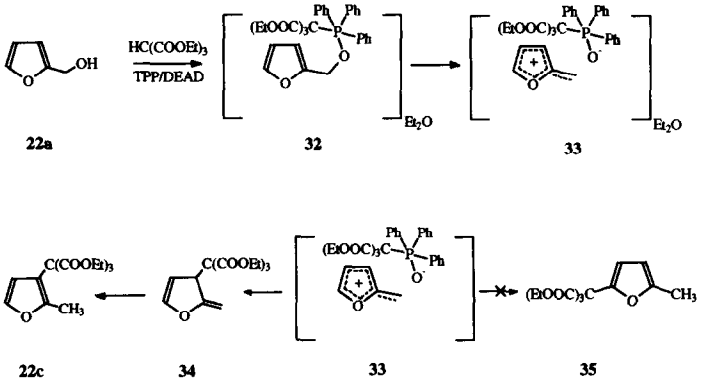
Alcohol	Product	Yield (%)	Procedure
$n\text{-}C_8H_{17}OH$ **(8a)**	$n\text{-}C_8H_{17}C(COOEt)_3$ **(8b)**	75	A
$n\text{-}C_{16}H_{33}OH$ **(9a)**	$n\text{-}C_{16}H_{33}C(COOEt)_3$ **(9b)**	81	A
$PhCH_2CH_2OH$ **(10a)**	$PhCH_2CH_2C(COOEt)_3$ **(10b)**	50	A
$PhCH_2OCH_2CH_2OH$ **(11a)**	$PhCH_2OCH_2CH_2C(COOEt)_3$ **(11b)**	55	A
$ClCH_2CH_2OH$ **(12a)**	$ClCH_2CH_2C(COOEt)_3$ **(12b)**	60	A
Ph_2CHCH_2OH **(13a)**	$Ph_2CHCH_2C(COOEt)_3$ **(13b)**	68	B
$PhCH_2OH$ **(14a)**	$PhCH_2C(COOEt)_3$ **(14b)**	73	A
3-MeO-$PhCH_2OH$ **(15a)**	3-MeO-$PhCH_2C(COOEt)_3$ **(15b)**	65	A
4-MeO-$PhCH_2OH$ **(16a)**	4-MeO-$PhCH_2C(COOEt)_3$ **(16b)**	53	A
2-NO_2-$PhCH_2OH$ **(17a)**	2-NO_2-$PhCH_2C(COOEt)_3$ **(17b)**	66	A
4-NO_2-$PhCH_2OH$ **(18a)**	4-NO_2-$PhCH_2C(COOEt)_3$ **(18b)**	80	A
 **(19a)**	 **(19b)**	78	A
 **(20a)**	 **(20b)**	80	A
 **(21a)**	 **(21b)**	62	A
 **(22a)**	 **(22b)**  **(22c)**	25 68	A

Alcohol	Product	Yield (%)	Procedure
 (**23a**)	 (**23b**)	70	A
	 (**23c**)	13	
 (**24a**)	 (**24b**)	78	B
Ph_2CHOH (**25a**)	$Ph_2CHC(COOEt)_3$ (**25b**)	30	A
 (**26a**)	 (**26b**)	70	A
$HOCH_2C{\equiv}CCH_2OH$ (**27a**)	$(EtOOC)_3CCH_2C{\equiv}CCH_2C(COOEt)_3$ (**27b**)	72	A
 (**28a**)	 (**28b**)	78	A
 (**29a**)	 (**29b**)	77	A
 (**30a**)	 (**30b**)	65	A
 (**31a**)	 (**31b**)	56	B

Mention must be made here that the allylic alcohols (*e.g.*, geraniol **28a**, (*E,E*)-farnesol **29a**, perillyl alcohol **30a**, cinnamyl alcohol **26a** and 2-butyne-1,4-diol **27a**) which could be susceptible to S_N2', are smoothly converted to the respective esters (arising from normal S_N2 displacement) without any loss in regiochemistry being observed. For purposes of solubility, the reaction of pyridine-2,6-dimethanol **23a**[16] was carried out in THF (conditions A), leading to the isolation not only of the expected **23b** (70%) but also of a by-product identified as **23c** (13%).[17] In sharp contrast, the reaction, under the same conditions, of furfuryl alcohol **22a**

gave predominantly **22c** (68%) along with only 25% of the expected **22b**. The origin of the abnormal regioselection in this process deserves some comment. The rationale of this noteworthy result is that the strong stabilizing effect of the 2-furyl substituent[18] encourages the formation of a rearranged product at the expense of the normal product (*ipso* substitution). Apparently, the reaction is initiated by heterolysis of the C-O bond of the pentacoordinated phosphorane **32** to give an intimate ion-pair **33** stabilized by the non-polar solvent Et_2O. Prior to the collapse of this ion pair, the nucleophile $C(COOEt)_3^-$ synfacially[19] attacks at the C-3 position, giving rise to the "abnormal" product **22c** through 1,3-hydrogen shift of the transient 2-methylene-2,3-dihydrofuran derivative **34** (Scheme 2).

Scheme 2



In contrast to the above mechanism, any nucleophile attack on the "free" 2-furylmethyl carbenium ion from the ion-pair would, in principle, take place at three different positions (*i.e.*, benzylic, C-3 and C-5). Several MO calculations have shown considerably less positive charge density at C-3 than at the methylene carbon or than C-5.[20] Thus, the failure to detect the expected "abnormal" compound **35** in the reaction mixture[21] supports a "tight" ion-pair mechanism although it might be argued that the "normal" **22b** is formed *via* a competing bimolecular pathway.Our investigations also highlighted the limitations of the Mitsunobu technology. It is well known that steric hindrance in secondary alcohols has a deleterious effect. In fact, our attempt to use application of TEMT as a proton donor (and nucleophile) on straight-chain (heptan-2-ol, octan-2-ol) or cyclic secondary alcohols (menthol, cyclohexanol) was unsuccessful.

Not surprisingly, reaction of benzylic secondary alcohols [(±)-1-phenylethanol **24a**, diphenylcarbinol **25a**] led to the expected adducts in 78% and 65% isolated yields, respectively (conditions B). Application of these conditions to (*S*)-(-)-ethyl lactate **31a** provided the tetraester **31b** $[\alpha]_D$ = - 19.8 (c = 1.68, EtOH) in 56% yield. To establish absolute configuration of **31b**, this was converted into the known 2-methylsuccinic acid by acidic hydrolysis (6N HCl, 18h reflux) followed by thermal decarboxylation.

The absolute (*S*)-(-)- configuration and 87 % ee of the product were assigned by comparing them with the value and the sign of the optical rotation of enantiopure (*S*)-(-)-2-methylsuccinic acid.[22] This finding demonstrated that alkylation of TEMT by (*S*)-(-)-ethyl lactate occurred with a predominant inversion of configuration, in accordance with the well documented bimolecular pathway of the Mitsunobu reaction.

CONCLUSION

The present work has shown that TEMT **7** can act as an efficient carbon-centered nucleophile under Mitsunobu conditions, thereby representing a suitable surrogate for diethyl malonate. Furthermore, TEMT offers crucial advantages over the classic malonates in its ability to a) avoid dialkylation, which normally plagues the monoalkylation with reactive halides or α,ω-dibromoalkanes, and b) withstand the presence of several functional groups. This approach seems well suited to access, under *neutral* and *extraordinarily mild* conditions, a wide variety of functionalised compounds.

EXPERIMENTAL SECTION

IR spectra (neat unless stated otherwise) were recorded on a Perkin Elmer 457 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured in deuterochloroform with a Bruker AC 200 (200 MHz and 50.3 MHz, respectively). Mass spectra were obtained with a VG 7070 EQ spectrometer (CI-MS, isobutane). Optical rotations were measured at 25 °C using a 10 cm cell on a Perkin Elmer 241 polarimeter. Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F254 (visualization with iodine or cerium(IV)-molybdate). Diethyl ether and tetrahydrofuran were distilled under nitrogen from lithium aluminum hydride. Melting points were determined on a Büchi 510 apparatus and are uncorrected. Organic solutions were dried over sodium sulphate and the products isolated by filtration and evaporation using a rotary evaporator operating at 15 torr. The reaction mixtures were all purified by silica gel chromatography; all new compounds are thick oils, except for **9b** and **25b**. Gas-liquid chromatographic analyses were run on a Dani 86.10 gaschromatograph, equipped with a OV1 column (temperature program: 40 °C 1 min, 5 °C/min → 120 °C, 120 °C 40 min) and retention times (Rt) were reported. Elemental combustion analyses were performed on Perkin Elmer 240 instrument and all new compounds gave satisfactory analyses (C ± 0.38%, H ± 0.30%).

All reactions were performed under a nitrogen atmosphere using flame-dried glassware.The alcohols used in these preparations were commercially available and were used without further purification, except for benzyl alcohol and 2-nitrobenzyl alcohol, respectively purified by distillation and crystallization to remove oxidation by-products.

1,1,1-Tris(ethoxycarbonyl)nonane (8b)

MS (CI) 345 ($M+H^+$) (Calc. for $C_{18}H_{32}O_6$ = 344); ^{1}H-NMR 4.26 q[6H] (J = 7.1 Hz), 2.11 m[2H], 1.50-1.15 m[15H], 1.29 t[9H] (J = 7.1 Hz), 0.88 bt[3H].

1,1,1-Tris(ethoxycarbonyl)heptadecane (9b)

White, waxy solid m.p. 40-40.5 °C (pentane); MS 457 ($M+H^+$) (Calc. for $C_{26}H_{48}O_6$ = 456); ^{1}H-NMR 4.26 q[6H] (J = 7.1 Hz), 2.10 m[2H], 1.6-1.1 m[28H], 1.28 t[9H] (J = 7.0 Hz); IR (KBr pellet) 1782, 1753, 1474, 1246, 1126, 1035 cm^{-1}.

1,1,1-Tris(ethoxycarbonyl)-3-phenylpropane (10b)

MS 337 ($M+H^+$) (Calc. for $C_{18}H_{24}O_6$ = 336); ^{1}H-NMR 7.31-7.20 m[5H], 4.29 q[6H] (J = 7.1 Hz), 2.82 m[2H], 2.42 m[2H], 1.32 t[9H] (J = 7.0 Hz).

1,1,1-Tris(ethoxycarbonyl)-3-benzyloxypropane (11b)

MS 367 ($M+H^+$) (Calc. for $C_{19}H_{26}O_7$ = 366); ^{1}H-NMR 7.35-7.28 m[5H], 4.48 s[2H], 4.23 q[6H] (J = 7.0 Hz), 3.75 t[2H] (J = 6.9 Hz), 2.52 t[2H] (J = 6.9 Hz), 1.26 t[9H] (J = 7.2 Hz).

3-Chloro-1,1,1-tris(ethoxycarbonyl)propane (12b)

MS 295-297 ($M+H^+$) (Calc. for $C_{12}H_{19}ClO_6$ = 294); ^{1}H-NMR 4.21 q[6H] (J = 7.2 Hz), 3.85 t[2H] (J = 6.0 Hz), 3.68 t[2H] (J = 6.1 Hz), 1.29 t[9H] (J = 7.1 Hz).

3,3-Diphenyl-1,1,1-tris(ethoxycarbonyl)propane (13b)

MS 413 ($M+H^+$) (Calc. for $C_{24}H_{28}O_6$ = 412); ^{1}H-NMR 7.33-7.22 m[10H], 4.49 t[1H] (J = 6.5 Hz), 3.95 q[6H] (J = 7.1 Hz), 3.05 d[2H] (J = 6.5 Hz), 1.16 t[9H] (J = 7.1 Hz).

1,1,1-Tris(ethoxycarbonyl)-2-phenylethane (14b)

MS 323 ($M+H^+$) (Calc. for $C_{17}H_{22}O_6$ = 322); ^{1}H-NMR 7.35-7.28 m [5H], 4.21 q[6H] (J = 7.1 Hz), 3.54 s[2H], 1.22 t[9H] (J = 7.2 Hz); IR (KBr pellet) 1715, 1581, 1306, 1088 cm^{-1}.

1,1,1-Tris(ethoxycarbonyl)-2-(3-methoxyphenyl)ethane (15b)

MS 353 ($M+H^+$) (Calc. for $C_{18}H_{24}O_7$ = 352); ^{1}H-NMR 7.17 t[1H] (J = 8.1 Hz), 6.87 bs[2H], 6.80 dd[1H] (J_1 = 8.0 Hz, J_2 = 7.0 Hz), 4.22 q[6H] (J = 7.2 Hz), 3.78 s[3H], 3.52 s[2H], 1.23 t[9H] (J = 7.2 Hz).

1,1,1-Tris(ethoxycarbonyl)-2-(4-methoxyphenyl)ethane (16b)

MS 353 ($M+H^+$) (Calc. for $C_{18}H_{24}O_7$ = 352); ^{1}H-NMR 7.20 ½AB[2H] (J_{AB} = 8.6 Hz), 6.78 ½AB[2H] (J_{AB} = 8.8 Hz), 4.20 q[6H] (J = 7.1 Hz), 3.77 s[3H], 3.47 s[2H], 1.23 t[6H] (J = 7.2 Hz); IR 1744, 1514, 1248, 1180, 1057, 862 cm^{-1}.

1,1,1-Tris(ethoxycarbonyl)-2-(2-nitrophenyl)ethane (17b)

MS 368 ($M+H^+$) (Calc. for $C_{17}H_{21}NO_8$ = 367); ^{1}H-NMR 7.98 d[1H] (J = 7.8 Hz), 7.53-7.50 m[2H], 7.46-7.36 m[1H], 4.22 q[6H] (J = 7.2 Hz), 4.03 s[2H], 1.24 t[9H] (J = 7.1 Hz).

1,1,1-Tris(ethoxycarbonyl)-2-(4-nitrophenyl)ethane (18b)

MS 368 ($M+H^+$) (Calc. for $C_{17}H_{21}NO_8$ = 367); ^{1}H-NMR 8.11 ½AB[2H] (J_{AB} = 8.7 Hz), 7.48 ½AB[2H] (J_{AB} = 8.8 Hz), 4.21 q[6H] (J = 7.2 Hz), 3.60 s[2H], 1.23 t[9H] (J = 7.2 Hz); IR 1740, 1530, 1368, 860 cm^{-1}.

1,1,1-Tris(ethoxycarbonyl)-2-(3,4-methylenedioxyphenyl)ethane (19b)

MS 367 ($M+H^+$) (Calc. for $C_{18}H_{22}O_8$ = 366); ^{1}H-NMR 6.81 m[1H], 6.70 m[2H], 5.91 s[2H], 4.22 q[6H] (J = 7.0 Hz), 3.45 s[2H], 1.24 t[9H] (J = 7.0 Hz).

1,1,1-Tris(ethoxycarbonyl)-2-(4-methyl-5-thiazolyl)propane (20b)

MS 358 ($M+H^+$) (Calc. for $C_{16}H_{23}NO_6S$ = 357); ^{1}H-NMR 8.64 s[1H], 4.31 q[6H] (J = 7.1 Hz), 3.04 m[2H], 2.44 s[3H], 2.38 m[2H], 1.32 t[9H] (J = 7.1 Hz).

1,1,1-Tris(ethoxycarbonyl)-2-(1-methyl-2-indolyl)ethane (21b)

MS 376 ($M+H^+$) (Calc. for $C_{20}H_{25}NO_6$ = 375); ^{1}H-NMR 7.52 d[1H] (J = 7.45 Hz), 7.39-7.02 m[4H], 4.25 q[6H] (J = 7.1 Hz), 3.72 s[2H], 3.71 s[3H], 1.22 t[9H] (J = 7.1 Hz); IR 1744, 1468, 1267, 1220, 1057 cm^{-1}; Rt = 60.78 min.

1,1,1-Tris(ethoxycarbonyl)-2-(2-furyl)ethane (22b)

MS 313 ($M+H^+$) (Calc. for $C_{15}H_{20}O_7$ = 312); ^{1}H-NMR 7.29 d[1H] (J = 1.9 Hz), 6.28 dd [1H] (J_1 = 3.1 Hz, J_2 = 1.9 Hz), 6.16 d[1H] (J = 3.3 Hz), 4.25 q[6H] (J = 7.1 Hz), 3.56 s[2H], 1.26 t[9H] (J = 7.1 Hz); ^{13}C-NMR 166.2, 150.0, 141.3, 110.3, 108.4, 62.2, 61.8, 31.5, 13.8.

1,1,1-Tris(ethoxycarbonyl)-1-(2-methyl-3-furyl)methane (22c)

MS 313 ($M+H^+$) (Calc. for $C_{15}H_{20}O_7$ = 312); ^{1}H-NMR 7.25 d[1H] (J = 2.0 Hz), 6.62 d[1H] (J = 1.9 Hz), 4.31 q[6H] (J = 7.1 Hz), 2.22 s[3H], 1.31 t[9H] (J = 7.1 Hz); ^{13}C-NMR 166.1, 151.0, 139.2, 112.5, 111.4, 65.4, 62.5, 13.8, 13.2.

2,6-Bis[1,1,1-tris(ethoxycarbonyl)methyl]pyridine (23b)

MS 568 ($M+H^+$) (Calc. for $C_{27}H_{37}NO_{12}$ = 567); ^{1}H-NMR 7.47 t[1H] (J = 7.7 Hz), 7.09 d[2H] (J = 7.7 Hz), 4.22 q[12H] (J = 7.1 Hz), 3.62 s[4H], 1.21 t[18H] (J = 7.1 Hz); IR 1740, 1454, 1370, 1304, 1250, 1223, 1064 cm^{-1}.

Diethyl 2-[(6-(1-(2,2,2-tris(ethoxycarbonyl)ethyl)pyridyl)methyl)]hydrazine-1,2-dicarboxylate (23c)

MS 498 ($M+H^+$) (Calc. for $C_{27}H_{37}NO_{12}$ = 497); ^{1}H-NMR 7.55 t[1H] (J = 7.7 Hz), 7.09 d[1H] (J = 7.9 Hz), 7.03 d[1H] (J = 7.8 Hz), 4.75 bs[1H], 4.34-4.14 m[12H], 3.72 s[2H], 1.28 m[6H], 1.20 t[9H] (J = 7.1 Hz).

(±)-1,1,1-Tris(ethoxycarbonyl)-1-phenylpropane (24b)

MS 337 ($M+H^+$) (Calc. for $C_{18}H_{24}O_6$ = 336); ^{1}H-NMR 7.45-7.38 m[2H], 7.31-7.21 m [3H], 4.17 m[6H], 3.86 q[1H] (J = 7.2 Hz), 1.51 d[3H] (J = 7.2 Hz), 1.20 t[9H] (J = 7.0 Hz).

1,1,1-Tris(ethoxycarbonyl)-2,2-diphenylethane (25b)

Colourless solid, m.p. 58 °C (hexane) (lit.[23] = 60 °C); MS 399 ($M+H^+$) (Calc. for $C_{23}H_{26}O_6$ = 398); ^{1}H-NMR 7.33-7.21 m[10H], 4.49 t[1H] (J = 6.5 Hz), 3.95 q[6H] (J = 7.1 Hz), 3.05 d[2H] (J = 6.5 Hz), 1.16 t[9H] (J = 7.1 Hz).

(*E*)-3,3,3-Tris(ethoxycarbonyl)-1-phenylbutene (26b)

MS 349 ($M+H^+$) (Calc. for $C_{19}H_{24}O_6$ = 348); ^{1}H-NMR 7.37-7.21 m[5H], 6.53-6.40 m[2H], 4.69 q[6H] (J = 7.2 Hz), 3.05 d[2H] (J = 6.0 Hz), 1.28 t[9H] (J = 7.2 Hz); IR 1740, 1466, 1265, 1219, 1061 cm^{-1}.

1,1,1,6,6,6-Hexakis(ethoxycarbonyl)-3-hexyne (27b)

MS 515 ($M+H^+$) (Calc. for $C_{24}H_{34}O_{12}$ = 514); ^{1}H-NMR 4.26 q[12H] (J = 7.0 Hz), 2.96 s[4H], 1.27 t[18H] (J = 7.1 Hz); IR 1743, 1271, 1198, 1068 cm^{-1}; Rt = 17.48 min.

(3*E*)-4,8-Dimethyl-1,1,1-tris(ethoxycarbonyl)-3,7-nonadiene (28b)

MS 369 ($M+H^+$) (Calc. for $C_{20}H_{32}O_6$ = 368); ^{1}H-NMR 5.33 t[1H] (J = 7.0 Hz), 5.06 m [1H], 4.25 q[6H] (J = 7.2 Hz), 2.85 d[2H] (J = 7.1 Hz), 2.00 m[4H], 1.66 s[3H], 1.62 s[3H], 1.58 s[3H], 1.26 t[9H] (J = 6.8 Hz); IR 1745, 1446, 1308, 1261, 1063 cm^{-1}; Rt = 51.68 min.

(3*E*,7*E*)-1,1,1-Tris(ethoxycarbonyl)-4,8,12-trimethyl-3,7,11-tridecatriene (29b)

MS 437 ($M+H^+$) (Calc. for $C_{25}H_{40}O_6$ = 436);^{1}H-NMR 5.34 td[1H] (J_1 = 7.2 Hz, J_2 = 2.0 Hz), 5.10 m[2H], 4.25 q[6H] (J = 7.2 Hz), 2.86 d[2H] (J = 7.2 Hz), 2.01 m[8H], 1.69 s[3H], 1.63 s [3H], 1.60 s[3H], 1.59 s[3H], 1.27 t[9H] (J = 7.2 Hz);IR 1742, 1446, 1302, 1261, 1062 cm^{-1}; Rt = 58.11 min.

1,1,1-Tris(ethoxycarbonyl)-2-(4-isopropenyl-1-cyclohexenyl)ethane (30b)

MS 367 ($M+H^+$) (Calc. for $C_{20}H_{30}O_6$ = 366); ^{1}H-NMR 5.54 m[1H], 4.70 m[2H], 4.25 q [6H] (J = 7.2 Hz), 2.94 s[2H], 2.25-1.60 m[6H], 1.72 s[3H], 1.29 t[9H] (J = 7.0 Hz); IR 1747, 1446, 1261, 1223, 1062 cm^{-1}; Rt = 55.13 min.

(2*S*)-(-)-1,1,1-2-Tetrakis(ethoxycarbonyl)-propane (31b)

MS 333 ($M+H^+$) (Calc. for $C_{15}H_{24}O_8$ = 332); ^{1}H-NMR 4.28 q[6H] (J = 7.1 Hz), 4.18 q [2H] (J = 7.1 Hz), 3.37 q[1H] (J = 7.3 Hz), 1.46 d[3H] (J = 7.4 Hz), 1.30 m[9H], 1.27 s[3H] (J = 7.1 Hz); $[\alpha]_D$ = - 19.8 (c = 1.68, EtOH).

REFERENCES AND NOTES

1. Mitsunobu, O.; Yamada, M. *Bull.Chem.Soc.Jpn* **1967**, *40*, 2380.
2. a) Mitsunobu,O. *Synthesis* **1981**, 1; b) Hughes, D.L. *Org.Reactions* **1972**, *42*, 335; c) Hughes, D.L. *Org.Prep.Proc.Int.* **1996**, *28*, 129.
3. a) Hughes, D.L.; Reamer, R.A.; Bergan, J.J.; Grabowski, E.J.I. *J.Am.Chem.Soc.* **1988**, *110*, 6487; b) Camp, D.; Jenkins, I.D. *J.Org.Chem.* **1989**, *54*, 3045; c) Camp, D.; Jenkins, I.D. *ibid.* **1989**, *54*, 3049; d) Camp, D.; Jenkins, I.D.*Aust.J.Chem.* **1992**, *45*, 47; e) Macor, J.E.; Wehner, J.M. *Heterocycles* **1993**, *35*, 349.
4. Falck, J.R.; Yu, J.; Cho, H.-S. *Tetrahedron Lett.***1994**, *35*, 5997.
5. Diethyl malonate reacts with benzyl alcohol through the agency of TPP-DEAD in only 2-3% yield (Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639).

6. See for example. Aesa, M.C.; Baan, G.; Novak, L.; Szantay, C. *Synthetic Commun.* **1996**, *26*, 909 and references cited.
7. Yu, J.; Falck, J.R.; Mioskowski, C. *J.Org.Chem.* **1992**, *57*, 3757.
8. Yu, J.; Lai, J.Y., Falck, J.R. *SYNLETT.* **1995**, 1127.
9. For a review on the chemistry of methanetricarboxylate esters: Newkome, G.R.; Baker, G.R. *Org.Prep. Proc.Int.* **1986**, *18*, 119.
10. Guthrie, J.P. *Can.J.Chem.* **1979**, *57*, 1177.
11. Newkome, G.R.; Yao, Z.-Q.; Baker, G.R.; Gupta, V.K. *J.Org.Chem.* **1985**, *50*, 2003.
12. Padgett, H.C.; Csendes, I.G.; Rapoport, H. *J.Org.Chem.* **1979**, *44*, 3492.
13. Bohme, H.; Hafner, L. *Chem.Ber.* **1966**, *99*, 281.
14. Arct, B.; Prelicz, D.; Witek, H. *Rocz.Chem.* **1967**, *41*, 683 (*Chem.Abstr.* **1967**, *67*, 54098q).
15. A number of other redox systems were examined (data not shown) including the use of Bu_3P and $(PhO)_3P$ *in lieu* of TPP and the use of DIAD (diisopropyl azodicarboxylate) *in lieu* of DEAD.
16. Throughout this paper, **a** and **b** designate the starting material and the expected Mitsunobu product, respectively.
17. Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, 1279.
18. Mitsunobu reaction on chiral non-racemic *p*-methoxy benzyl alcohols or alkyl furylmethanols are prone to esterification with substantial racemisation due to the stability of the incipient carbocation which promotes the unimolecular pathway (Brown, R.F.C.; Jackson, W.R.; McCarthy, T.D.; *Tetrahedron Lett.* **1993**, *34*, 1195; Warmerdam, E.G.J.C.; Brussee, J.; Kruse, C.G.; van der Gen, A. *Tetrahedron Lett.* **1993**, *34*, 1063).
19. Synfacial attack *i.e.,* the nucleophile enters from the same side as the leaving group departs (Jefford, C.W.; Sweeney, A.; Hill, D.T., Delay, F.; *Helv.Chim.Acta* **1971**, *54*, 1691).
20. a) Streitwieser, A. In ' Molecular Orbital Theory for Organic Chemists' Wiley, New York, N.Y., 1961; b) Herndon, W.C., Feuer, J. *J.Org.Chem.* **1968**, *33*, 417; c) Divald, S.; Chun, M.C.; Joullié, M.M. *J. Org. Chem.* **1976**, *41*, 2835.
21. For related examples, see Ref. 20c; Yamamoto, F.; Hiroyuki, M.; Oae, S. *Heterocycles* **1975**, *3*, 1.
22. Kurihara, T.; Sugizaki, M.; Kime, I.; Wada, M.; Mitsunobu, O.; *Bull. Chem. Soc. Jpn* **1981**, 54, 2107.
23. Rakus, K.; Verevkin, S.P.; Keller, M.; Beckhaus, H.-D.; Rüchardt, C. *Liebigs Ann.* **1995**, 1483.

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