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^{1}H NMR Correlation of Chiral 3-Phenylbutanoates for the Determination of Absolute Stereochemistry of Chiral Alcohols

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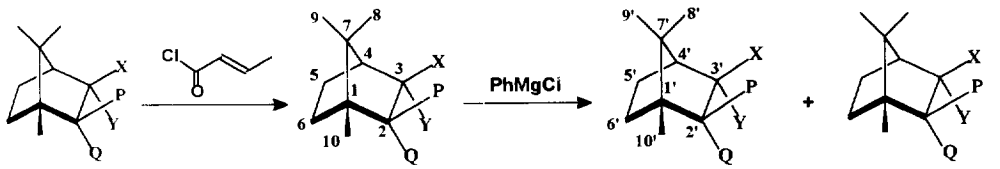
Abstract : A study of diastereoselective 1,4-addition of phenyl Grignard has been attempted on some chiral crotonates. The Π-facial selectivities in these reactions have been determined on the basis of specific rotations of the hydrolysis product, namely 3-phenyl butanoic acid (3PBA). Correlation of these results with the results obtained from ^{1}H NMR shieldings arising due to phenyl anisotropy, has led to conformational correlation model for the determination of absolute stereochemistry of chiral alcohols.

The chiral pool of natural products has been widely used for total syntheses of natural products and has been applied for evolving new methodology for asymmetric C-C bond formation. A variety of chiral enoates including α,β-unsaturated-esters, -amides, -N-enoyl sultams and α,β-ethylenic sulfoxides[1] have been utilized. Of the cheaply available members of the chiral pool, camphor has been well exploited.[2] The success in the use of camphor is due to its rigid structure and the possibility of appropriate derivatization to allow greater stereoselection.[3-6] In line with above studies we have synthesized chiral crotonates **7-12** starting with appropriate isoborneols and borneols, **1-6**.[7]

1,4-addition reactions to crotonates, **7-12**, were studied with Grignard reagents obtained from phenyl bromide, both with and without the use of Cu(I) (Scheme 1). Whereas the sulfide derivatives **7-9** did not react at lower temperatures (-78 and -40 °C) and gave a multiplicity of products at -10 °C, **10-12,** gave the required adducts only at -10 °C. In the case of **11**, the reaction took place at -10 °C in the presence of Cu(I) but was found to be sluggish and was therefore carried out at 0 °C.

The ^{1}H NMR spectra of products obtained in the Cu(I) catalysed reactions showed them each to be a mixture of two compounds, epimeric at newly formed stereogenic center. These diastereomers were not separable by column chromatography. The two most upfield methyl signals, in each of these fractions, were well resolved and assigned to 10'-H_3 resonances. From the integration of these signals, the diastereomeric ratios of **13**:**14**, **15**:**16** and **17**:**18** were calculated to be 66:34, 40:60 and 57:43, respectively (Table 1). The absolute stereochemistry of the diastereomeric compounds, **13-18**, were determined from the sign of rotation of 3-phenylbutanoic acid (3PBA) obtained on hydrolysis of their respective 1,4-adduct mixtures with KOH in ethanol. The 3PBA obtained from phenyl adducts of **10**, **11** and **12** showed .specific rotation of $[\alpha]^{26}_D$ = +12.4 (c 9, benzene), $[\alpha]^{26}_D$ = -10.2(c 5.44, benzene), and $[\alpha]^{26}_D$ = +5.6 (c 7.13, benzene), respectively. Hence it was concluded that the 1,4-additions proceeded with the preferential formation of S-(+)-3PBA derivatives of **4** and **6** and R-(-)-3PBA derivative of **5**. The diastereomeric ratios of the epimers, thus calculated from the known

specific rotation of R-(-)-3PBA[2] {$[\alpha]^{25}_D$ = -56.8(c 9, benzene)}, were found to be comparable to those obtained by ^{1}H NMR spectroscopy.



1 : P=OH; Q=Y=H; X=R^1
2 : Q=OH; P=X=H; Y=R^1
3 : P=OH; Q=X=H; Y=R^1
4 : P=OH; Q=Y=H; X=R^2
5 : Q=OH; P=X=H; Y=R^2
6 : P=OH; Q=X=H; Y=R^2

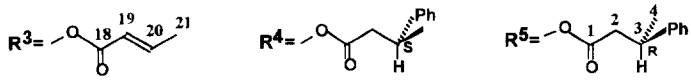
7 : P=R^3; Q=Y=H; X=R^1
8 : Q=R^3; P=X=H; Y=R^1
9 : P=R^3; Q=X=H; Y=R^1
10 : P=R^3; Q=Y=H; X=R^2
11 : Q=R^3; P=X=H; Y=R^2
12 : P=R^3; Q=X=H; Y=R^2

13 : P=R^4; Q=Y=H; X=R^2
15 : Q=R^4; P=X=H; Y=R^2
17 : P=R^4; Q=X=H; Y=R^2

14 : P=R^5; Q=Y=H; X=R
16 : Q=R^5; P=X=H; Y=R
18 : P=R^5; Q=X=H; Y=R

Where,

R^1=CH_2SPh
R^2=CH_2SO_2Ph



Scheme 1 : 1,4-Addition of phenylmagnesium bromide to chiral crotonates.

Table 1 : Diastereomeric composition of 1,4 adducts.

	With Cu(I)	Without Cu(I)
13:14	63:34	24:76
15:16	40:60*	61:39
17:18	57:43	40:60

* : At O^o C.

The ^{1}H NMR spectra of the diastereomeric mixtures obtained on 1,4-addition of phenyl Grignard to crotonates **10-12** in the absence of Cu(I) showed reversal of diastereoselectivity in all the three cases *vis-a-vis* the reaction products in the corresponding reaction in presence of Cu(I). This result is significant indicating a dependence of transition state geometry of crotonate moieties on the type of cation(s) present in the reaction mixture. Similar results were obtained earlier with phenyl Grignard addition to crotonate esters of menthol and 1,2-O-isopropylidene-5-deoxy-D-xylose[8,9] as well. These results could be explained by assuming a preferred transition state geometry of crotonates similar to that suggested by Oppolzer et. al[3,4,6] for addition of $RCu.BF_3$ complex to crotonates, wherein C=O double bond is *syn* with respect to the alkoxymethine bond. Since the approach of the addend to the enoates from the side of phenylsulfonylmethyl group is hindered, the addition occurs preferably from opposite side. On the basis of structures of the major diastereomers in these reactions, the Grignard reactions occur with enoates preferentially in *s-cis* conformation in the absence of Cu(I) and *s-trans* conformation in the presence of Cu(I). Although the conformational preferences seem to arise due to weak complexation of cations with the enoate moieties, the poor selectivity in these reactions indicate substantial mobility of the enoate moieties at the experimental conditions.

Another result was apparent from the ^{1}H NMR spectra of the diastereomeric mixtures. Against the closely comparable 10'-H_3 resonance positions of crotonates, 3-chloropropionates[6] and acrylates[6], the 10'-H_3 resonances of 3-phenylbutanoates obtained from same bornane alcohols were distinctly shielded. The shielding in the latter cases was due to the anisotropy observed over eight bond distance and caused by the newly introduced aryl groups. Further, even amongst the two 3-phenylbutanoate diastereomers the observed anisotropy was non identical with a significant chemical shift nonequivalence ($\Delta\delta$) of their 10'-H_3 signals. Since the stereogenic center of 3PBA was responsible for the observed $\Delta\delta$, the above observation clearly indicated that enantiopure 3PBA would make a good chiral derivatizing agent (CDA) for determination of the enantiomeric composition of chiral alcohols by ^{1}H NMR spectroscopy.

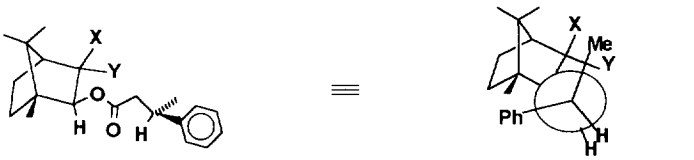
The differential shieldings amongst the diastereomers were attributed to different time average conformational orientations of the 3-phenylbutanoate molecular fragments. Interestingly there was an observable pattern of shieldings for these diastereomers. The shieldings of 10'-H_3 was more pronounced in (R)- 3-phenylbutanoate derivatives (**14** and **18**) than their (S)-3-phenylbutanoate derivatives (**13** and **17**) for isoborneol esters and for (S)-3-phenylbutanoate derivative (**15**) than its (R)-epimer (**16**) for borneol ester. This strongly indicated a possible ^{1}H NMR correlation for determination of absolute configuration of alcohol provided the absolute configuration of 3-PBA was known and *vice-a-versa*.

On the basis of the observed trend in the shielding patterns of 10'-H_3 of various adducts synthesized during the 1,4-addition reactions, a conformational correlation model is proposed for 3PBA for the determination of absolute configuration of the diastereomers, **13-18** (Figure 1). Similar conformational correlation models have been suggested earlier using α-(methoxy)-α-(trifluoromethylphenyl) acetic acid (MTPA)[10] and O-methylmandelic acid[11] earlier. A fully extended chain with alkoxy methine proton eclipsed with carbonyl oxygen is expected, in line with models for (R)-MTPA and (R)-O-methylmandelic acid derivatives. The methine proton at the stereogenic center on 3PBA is also assumed to be eclipsed with the carbonyl group. Using this model, the protons shielded due to phenyl anisotropy can be determined by "extended Newman projection", T_1. This model allows for greater shielding of 10'-H_3 of (R)-3-phenylbutanoates, **14** and **18** (T_2), than in their corresponding epimeric (S)-3-phenylbutanoates, **13** and **17** and similarly in (S)-3-phenylbutanoate **15** (T_3) than in **16**, consistent with the observed results. Conversely, knowing the absolute configuration of 3PBA, it is possible to determine the absolute configuration of the alcohols.

To check the predictability of this model (T_1), 3PBA partially enhanced in S-(+)-isomer, was condensed with 1,2:5,6-di-O-acetylidene-α-D-glucofuranose (**19**) (Scheme 2). An inseparable mixture of epimers **20** and **21** were formed. In conformity with the model, it was observed that both 2-H and 3-H resonances of the major diastereomer **20** (formed from the S-(+)-PBA; T_4) were more shielded than the corresponding proton resonances from **21**. Validity of the model was further established by condensation of racemic 3PBA with open chain racemic 2-butanol (**22**). A set of two methyl signals (1'-H_3 and 4'-H_3) each for the two diastereomers **23** (R^*R^*) and **24** (R^*S^*), could be distinguished but could not be assigned specifically to either of the two diastereomers. It was however possible to assign these peaks only on the basis of model T_5 by which the most shielded methyl triplet and most deshielded methyl doublet were assigned to **23**. These assignments were confirmed by condensation of commercially available (S)-butan-2-ol and (S)-3PBA, which lent credence to the

proposed model (10% formation of R^*S^* derivative(s) was observed because of optical impurities in the commercial samples).

T_1 : Conformational correlation model for S-(+)-3PBA.



13 : X = $-CH_2SO_2Ph$; Y = H
17 : X = H; Y = $-CH_2SO_2Ph$

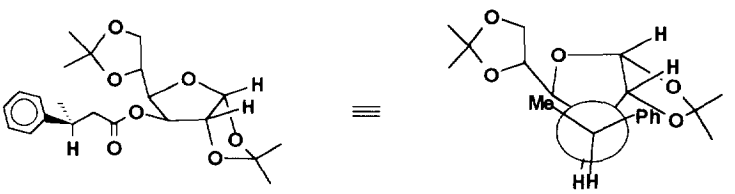
13 : X = $-CH_2SO_2Ph$; Y = H
17 : X = H; Y = $-CH_2SO_2Ph$

T_2 : Greater shielding of 10'-H_3 of S-(+)-3PBA derivatives of 13 and 17.

16 : X = $-CH_2SO_2Ph$

16 : X = $-CH_2SO_2Ph$

T_3 : Greater shielding of 10'-H_3 of R-(-)-3PBA derivative of 16.

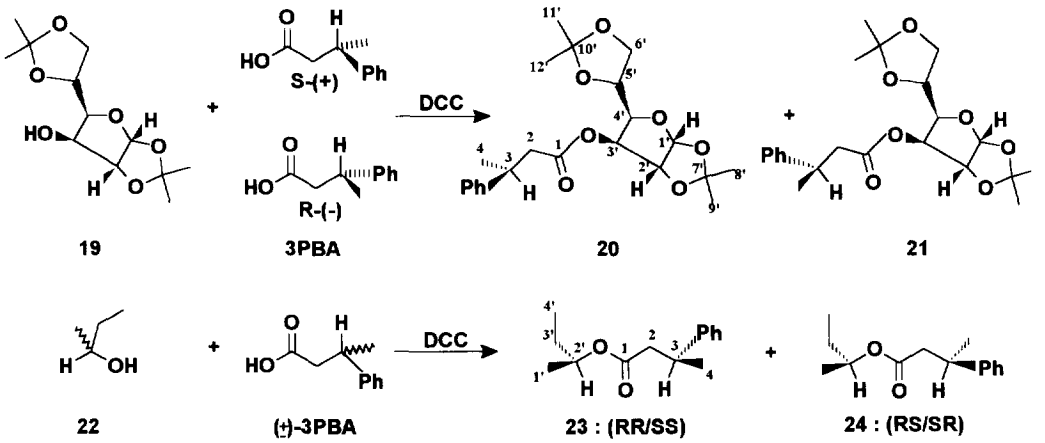


T_4 : Greater shielding of 3'-H and 4'-H of S-(+)-3PBA derivative of 20.

T_5 : Greater shielding of 4'-H_3 of S-(+)-3PBA derivative of 23.

Figure 1 : ^1H NMR conformational correlation model for 3PBA.

To further our claim that the observed shielding was due to conformational features of 3-phenylbutanoic acid fragment with respect to the alcohol units in the various molecules, temperature dependent ^1H NMR studies were undertaken. With decrease in temperature, there was an increase of $\Delta\delta$ values (Table 2). These results supported the suggested model and indicated that the "extended Newman projection" of the groups in the time average structures compare closely with those visualized from the proposed conformational correlation model.



Scheme 2

Table 2 : Temperature dependent ^{1}H NMR chemical shift non equivalence (Δδ) under phenyl anisotropy.

°C	13-14 10'-H_3	16-15 10'-H_3	17-18 10'-H_3	20-21 1'-H	23-24 1'-H_3	23-24 4'-H_3
40	-	0.09	0.10	0.17	0.05	0.05
30	0.16	0.10	0.11	0.18	0.06	0.06
20	0.16	0.11	0.11	0.20	0.06	0.06
10	0.17	0.11	0.12	0.22	0.06	0.06
5	0.18	0.11	0.12	0.23	-	-
0	0.18	0.11	-	0.24	0.06	0.07
-10	-	-	-	-	0.07	0.07
-20	-	-	-	-	0.07	0.08
-40	-	-	-	-	0.08	0.09

The efficacy of 3PBA as CDA was found to be poor for the derivatization of butan-2-ol in comparison to O-methyl mandelic acid and MTPA.[10a,12] However, for the other pairs of diastereomeric esters of 3PBA studied, the Δδ values between the appropriate proton resonances was substantial. There are certain advantages of use of 3PBA over the other CDAs for determination of absolute stereochemistry. As against the mandelic acid derived CDAs namely O-methyl mandelic acid[11] and O-acetyl mandelic acid[13] racemization of 3PBA is not possible under the normal esterification conditions. Also, both the isomers of 3PBA are commercially available and are much cheaper than MTPA. Thus, with the availability of high resolution NMR instruments, the use of 3PBA and its variants should be an alternative choice for determination of absolute configuration of alcohols. The utility of 3PBA with chiral amines has still to be ascertained though.

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EXPERIMENTAL :

^1H and ^{13}C NMR spectra were obtained at 300 MHz and 75 MHz, receptively, in CDCl using a Varian VXR 300S. IR spectra were recorded on Perkin-Elmer 681 spectrometer. Mass spectra were recorded using Shimadzu-QP1000. Optical rotations were obtained on Jasco DIP-370 in 10mm glass cell. Melting points recorded are uncorrected. "#" have been used in the representation of ^{13}C NMR data to indicate interchangeable carbon assignments.

General method of syntheses of crotonates :

Alcohol (1 mmol) and crotonyl chloride (1.3 mmol) were dissolved in dry benzene (5-10 ml) and refluxed for ~24 h. The disappearance of starting material on tlc marked the completion of reaction. The benzene layer was washed with Na_2CO_3 solution, water and brine and then dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum and chromatography of the crude sample gave required product.

Synthesis of 10

[1R-(1β,2β,3β,4β)]-3-phenylsulphonylmethyl-1,7,7,-trimethylbicyclo[2.2.1]hept-2-yl (E)-but-2-enoate (**10**) was obtained from [1R-(1β,2β,3β,4β)]-3-phenylsulfonylmethyl-1,7,7,-trimethylbicyclo[2.2.1]heptan-2-ol (**4**) in ~100% yield. IR (KBr) ν 1720, 1655, 1585, 1310, 1175,1155, 755, 695 cm^{-1}. MS : 376 [M^+]. $[\alpha]^{25}_D$ = +25.9(c 1.40; chloroform). ^1H NMR (δ) : 0.77 (s; 3H, 10-H_3), 0.80 (s; 3H, 9-H_3), 1.02 (s; 3H, 8-H_3), 0.98-1.11 (m; 1H, 5n-H), 1.21 (ddd, J = 4.4 Hz, 9.2 Hz, 13.2 Hz; 1H, 6n-H), 1.48-1.57 (m; 1H, 6x-H), 1.67-1.78 (m; 1H, 5x-H), 1.86 (d, J = 4 Hz; 1H, 4-H), 1.89(dd, J = 1.7 Hz, 7.0 Hz; 3H, 21-H_3), 2.32 (dt, J = 4.9 Hz, 8.6 Hz; 1H, 3n-H), 3.19-3.35 (m; 2H, 11-H_2), 4.92 (d; J = 8.6 Hz; 1H, 2n-H), 5.77 (dq, J = 1.6 Hz, 15.6 Hz; 1H, 19-H), 6.91 (dq, J = 7.0 Hz, 15.6 Hz; 1H, 20-H), 7.53-7.59(m; 2H, 14-H and 16-H), 7.63-7.68 (m; 1H, 15-H), 7.85-7.89 (m; 2H, 13-H and 17-H).

Synthesis of 11

[1R-(1β,2α,3α,4β)]-3-phenylsulfonylmethyl-1,7,7,-trimethylbicyclo[2.2.1]hept-2-yl 3-(E)-but-2-enoate (**11**) was obtained from [1R-(1β,2α,3α,4β)]-3-phenylsulfonylmethyl-1,7,7,-trimethylbicyclo[2.2.1]heptan-2-ol (**5**) in 99% yield. mp : 117-118 C. IR (KBr) : 1720, 1660, 1640, 1585, 1310, 1265, 1185, 1155, 755, 695 cm^{-1}. MS : 376 [M^+]. $[\alpha]^{25}_D$ = +7.91(c 1.27; chloroform). ^1H NMR (δ) : 0.76 (s; 3H, 8-H_3), 0.91 (s; 3H), 0.94 (s; 3H), 1.20-1.29 (m; 1H, 6x-H), 1.39-1.48 (m; 2H, 5n-H), 1.58-1.79 (m; 2H, 5x-H and 6n-H), 1.89 (dd, J = 1.6 Hz, 7.0 Hz; 3H, 21-H_3), 1.94 (t, J = 4.0 Hz; 1H, 4-H), 2.76-2.84 (m; 1H, 3x-H), 3.06-3.20 (m; 2H, 11-H_2), 5.11 (dd, J = 1.8 Hz, 10.3 Hz; 1H, 2x-H), 5.81 (dq, J = 1.6 Hz, 15.5 Hz; 1H, 19-H), 6.95 (dq, J = 7.0 Hz,15.5 Hz; 1H, 20-H), 7.52-7.58 (m; 2H, 14-H and 16-H), 7.62-7.67 (m; 1H, 15-H), 7.85-7.89 (m; 2H, 13-H and 17-H).

Synthesis of 12

[1R-(1β,2β,3α,4β)]-3-phenylsulfonylmethyl-1,7,7,-trimethylbicyclo[2.2.1]hept-2-yl (E)-but-2-enoate (**12**) was obtained from [1R-(1β,2β,3α,4β)]-3-phenylsulfonylmethyl-1,7,7,-trimethylbicyclo[2.2.1]heptan-2-ol (**6**) in 97% yield. IR (Neat) ν : 1715, 1655, 1585, 1310, 1185, 1155, 750, 695 cm^{-1}. MS : 376 [M^+]. ^1H NMR (δ) : 0.79 (s; 3H, 10-H_3), 0.89 (s; 3H, 9-H_3), 1.05 (s; 3H, 8-H_3), 1.05-1.11 (m; 1H, 6n-H), 1.33-1.41 (m; 1H, 5n-H), 1.53-1.68 (m; 2H, 5x-H and 6x-H), 1.88 (dd, J = 1.7 Hz, 7.0 Hz; 3H, 21-H_3), 2.03 (t, J = 3.9 Hz; 1H, 4-H), 2.68-2.74 (m; 1H, 3x-H), 3.21 (dd, J = 9.9 Hz, 14.1 Hz; 1H, 11a-H), 3.62 (dd, J = 4.8 Hz, 14.1 Hz; 1H, 11b-H), 4.31 (d, J = 4.2 Hz; 1H, 2n-H), 5.78 (dq, J = 1.7 Hz, 15.6 Hz; 1H, 19-H), 6.89 (dq, J = 7.0 Hz, 15.6 Hz; 1H, 20-H), 7.51-7.58 (m; 2H, 14-H and 16-H), 7.60-7.66 (m; 1H, 15-H), 7.89-7.93 (m; 2H, 13-H and 17-H).

General procedure for Grignard addition reaction

Grignard reagent was obtained from Mg (0.4 mmol) and phenylbromide (0.44 mmol) in dry ether (10 ml) under argon atmosphere at ambient temperature. CuCl (0.15 mmol) was then added only if the reaction was studied under the influence of Cu(I). The reagent so formed was cooled to -10 °C and to this stirred mixture, a solution of crotonate (0.1 mmol) dissolved in ether (~3 ml) was added drop wise. The reaction was quenched after 3 h with 2N NH_4Cl solution and an excess of NH_3 solution was then added to it. The reaction mixture was

extracted with ether, washed with water and brine, and dried over anhydrous Na_2SO_4. The crude obtained on removal of solvent under vacuum was chromatographed to get the required products.

Synthesis of 13 and 14 :[1R-[1β,2β(3R),3β,4β]]-3-phenylsulfonylmethyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl 3-phenylbutanoate (**13**) and [1R-[1β,2β(3S),3β,4β]]-3-phenylsulfonylmethyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl 3-phenylbutanoate (**14**) were obtained as a mixture from **10** in 8% yield in the absence of CuCl and in 83% yield in presence of CuCl.

Analysis of 13 and 14
IR ($CHCl_3$) ν : 1730, 1600, 1585, 1395, 1380, 705, 690 cm^{-1}. MS : 454 [M^+].

NMR analysis of 13
^{1}H NMR (δ) : 0.70 (s; 10'-H_3), 0.77 (s; 9'-H_3), 0.94 (s; 8'-H_3), 1.28(d, J = 7.0 Hz; 4-H_3), 1.83 (d, J = 4.0 Hz; 4'-H), 4.85 (d, J = 8.7 Hz; 2n-H). ^{13}C NMR (δ) : 11.00 (q; 1C, 10'-C), 20.88 (q; 1C, 8'-C), 21.21 (q; 1C, 9'-C), 22.38 (q; 1C, 4-C), 28.90 (t; 1C, 5'-C), 32.76(t; 1C, 6'-C), 36.37 (d; 1C, 3-C), 42.19(d; 1C, 3'-C), 42.74 (t; 1C, 2-C), 47.54 (s; 1C, 1'-C$^{\#}$), 49.52 (d; 1C, 4'-C), 49.85 (s; 1C, 7'-C$^{\#}$), 56.98 (t; 1C, 11'-C), 80.75 (d; 1C, 2'-C), 126.56 (d; 3C, 6-C, 8-C and 10-C), 127.98 (d; 2C, 14'-C and 16'-C), 128.55 (d; 2C, 7-C and 9-C), 129.23 (d; 2C, 13'-C and 17'-C), 133.62 (d; 1C, 15'-C), 139.17(s; 1C, 12'-C), 145.32 (s; 1C, 5-C), 171.31(s; 1C, 1-C).

NMR analysis of 14
^{1}H NMR (δ) : 0.54 (s; 10'-H_3), 0.74 (s; 9'-H_3), 0.92(s; 8'-H_3), 1.28 (d, J = 7.0 Hz; 4-H_3), 1.79 (d, J = 4.0 Hz; 4'-H), 4.85 (d, J = 8.7 Hz; 2n-H). ^{13}C NMR (δ) : 11.28 (q; 1C, 10'-C), 20.88(q; 1C, 8'-C), 21.21(q; 1C, 9'-C), 22.38 (q; 1C, 4-C), 28.90 (t; 1C, 5'-C), 32.76 (t; 1C, 6'-C), 36.26 (d; 1C, 3-C), 42.19 (d; 1C, 3'-C), 42.57 (t; 1C, 2-C), 47.54 (s; 1C, 1'-C$^{\#}$), 49.63 (d; 1C, 4'-C), 49.85 (s; 1C, 7'-C$^{\#}$), 56.79 (t; 1C, 11'-C), 80.86 (d; 1C, 2'-C), 126.56 (d; 3C, 6-C, 8-C and 10-C), 127.98 (d; 2C, 14'-C and 16'-C), 128.55 (d; 2C, 7-C and 9-C), 129.23 (d; 2C, 13'-C and 17'-C), 133.62 (d; 1C, 15'-C), 139.17(s; 1C, 12'-C), 145.32(s; 1C, 5-C), 171.44 (s; 1C, 1-C).

Synthesis of 15 and 16
[1R-[1β,2α(3R),3α,4β]]-3-phenylsulfonylmethyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl 3-phenylbutanoate (**15**) and [1R-[1β,2α(3S),3α,4β]]-3-phenylsulfonylmethyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl 3-phenylbutanoate (**16**) were obtained as a mixture from **11** in 16% yield in the absence of CuCl and in 53% yield in the presence of CuCl.

Analysis of 15 and 16
IR ($CHCl_3$) ν : 1730, 1605, 1585, 700, 690 cm^{-1}. MS : 454 [M^+].

NMR analysis of 15
^{1}H NMR (δ) : 0.56 (s, 10'-H_3), 1.27 (d, J = 7.0 Hz; 4-H_3), 1.85 (t, J = 4.4 Hz; 4'-H), 3.24 (br. sextet, J = 7.2 Hz; 3-H), 5.03 (dd, J = 2.0 Hz, 10.1 Hz; 2'x-H). ^{13}C NMR (δ) : 13.52 (q; 1C, 10'-C), 18.37 (q; 1C, 8'-C), 19.59 (q; 1C, 9'-C), 20.31 (t; 1C, 5'-C), 22.40 (q; 1C, 4-C), 26.46 (t; 1C, 6'-C), 33.71 (d; 1C, 3'-C), 36.45 (d; 1C, 3-C), 42.61 (t; 1C, 2-C), 46.93 (s; 1C, 1'-C$^{\#}$), 48.34 (d; 1C, 4'-C), 49.86 (s; 1C, 7'-C$^{\#}$), 53.34 (t; 1C, 11'-C), 77.36 (d; 1C, 2'-C), 126.48 (d; 1C, 8-C), 126.59 (d; 2C, 6-C and 10-C), 127.82 14'-C and 16'-C), 128.51 (d; 2C, 7-C and 9-C), 129.20 (d; 2C, 13'-C and 17'-C), 133.54 (d; 1C, 15'-C), 139.81 (s; 1C, 12'-C), 145.36 (s; 1C, 5-C), 172.00 (s; 1C, 1-C).

NMR analysis of 16
^{1}H NMR (δ) : 0.66 (s; 10'-H_3), 1.27 (d, J = 7.0 Hz; 4-H_3), 1.88 (t, J = 4.3 Hz; 4'-H), 3.24 (br. sextet, J = 7.2 Hz; 3-H), 5.05 (dd, J = 2.0 Hz, 10.3 Hz; 2'x-H). ^{13}C NMR (δ) : 13.37 (q; 1C, 10'-C), 18.37 (q; 1C, 8'-C), 19.59 (q; 1C, 9'-C), 20.31 (t; 1C, 5'-C), 22.52 (q; 1C, 4-C), 26.40 (t; 1C, 6'-C), 33.71 (d; 1C, 3'-C), 36.56 (d; 1C, 3-C), 42.78 (t; 1C, 2-C), 46.93 (s; 1C, 1'-C$^{\#}$), 48.42 (d; 1C, 4'-C), 49.86 (s; 1C, 7'-C$^{\#}$), 53.44 (t; 1C, 11'-C), 77.36 (d; 1C, 2'-C), 126.48 (d; 1C, 8-C), 126.59 (d; 2C, 6-C and 10-C), 127.82 (d; 2C, 14'-C and 16'-C),

128.51 (d; 2C, 7-C and 9-C), 129.20 (d; 2C, 13'-C and 17'-C), 133.54 (d; 1C, 15'-C), 139.81 (s; 1C, 12'-C), 145.36 (s; 1C, 5-C), 172.00 (s; 1C, 1-C).

Synthesis of 17 and 18

[1R-[1β,2β(3R),3α,4β)]-3-phenylsulfonylmethyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl 3-phenylbutanoate (**17**) and [1R-[1β,2β(3S),3α,4β)]-3-phenylsulfonylmethyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl 3-phenylbutanoate (**18**) were obtained as a mixture from **12** in 16% yield in the absence of CuCl and in 66% yield in the presence of CuCl.

Analysis of 17 and 18

IR $CHCl_3$) ν : 1725, 1600, 1585, 1395, 1375, 705, 690 cm^{-1}. MS : 454 [M^+].

NMR analysis of 17

^1H NMR (δ) : 0.71 (s; 10'-H_3), 0.84 (s; 9'-H_3), 0.93 (s; 8'-H_3), 1.25 (d, J = 7.0 Hz; 4-H_3), 1.97 (t, J = 3.5 Hz; 4'-H), 3.15 (dd, J = 10.1 Hz, J = 14.0 Hz; 11' a-H), 3.52 (dd, J = 4.9 Hz, 14.0 Hz; 11'b-H), 4.21(d, J = 4.1 Hz; 2'n-H). ^{13}C NMR (δ) : 11.05 (q; 1C, 10'-C), 19.13 (q; 1C, 8'-C), 20.26 (q; 1C, 9'-C), 20.31(t; 1C, 5'-C), 21.99 (q; 1C, 4-C), 33.74 (t; 1C, 6'-C), 36.51 (d; 1C, 3-C), 41.68 (d; 1C, 3'-C), 42.84 (t; 1C, 2-C), 47.77 (s; 1C, 1'-$C^{\#}$), 48.16 (d; 1C, 4'-C), 48.94 (s; 1C, 7'-$C^{\#}$), 56.55 (t; 1C, 11'-C), 85.18 (d; 1C, 2'-C), 126.33 (d; 1C, 8-C), 126.62 (d; 2C, 6-C and 10-C), 127.75 (d; 2C, 14'-C and 16'-C), 128.46 (d; 2C, 7-C and 9-C), 129.13 (d; 2C, 13'-C and 17'-C), 133.47 (d; 1C, 15'-C), 139.93 (s; 1C, 12'-C), 145.40 (s; 1C, 5-C), 171.97 (s; 1C, 1-C).

NMR analysis of 18

^1H NMR (δ) : 0.60 (s; 10'-H_3), 0.83 (s; 9'-H_3), 0.97 (s; 8'-H_3), 1.26 (d, J = 7.0 Hz; 4-H_3), 1.97 (t, J = 3.5 Hz; 4'-H), 3.16 (dd, J = 9.8 Hz, J = 14.0 Hz; 11'a-H), 3.51 (dd, J = 5.0 Hz, 14.0 Hz; 11'b-H), 4.21 (d, J = 4.1 Hz; 2'n-H). ^{13}C NMR (δ) : 11.28 (q; 1C, 10'-C), 19.13 (q; 1C, 8'-C), 20.26 (q; 1C, 9'-C), 20.31(t; 1C, 5'-C), 21.99 (q; 1C, 4-C), 33.79 (t; 1C, 6'-C), 36.40 (d; 1C, 3-C), 41.72 (d; 1C, 3'-C), 42.84 (t; 1C, 2-C), 47.77 (s; 1C, 1'-$C^{\#}$), 48.13 (d; 1C, 4'-C), 48.89 (s; 1C, 7'-$C^{\#}$), 56.49 (t; 1C, 11'-C), 85.31 (d; 1C, 2'-C), 126.40 (d; 1C, 8-C), 126.56 (d; 2C, 6-C and 10-C), 127.75 (d; 2C, 14'-C and 16'-C), 128.46 (d; 2C, 7-C and 9-C), 129.13 (d; 2C, 13'-C and 17'-C), 133.47 (d; 1C, 15'-C), 139.93 (s; 1C, 12'-C), 145.40 (s; 1C, 5-C), 172.05 (s; 1C, 1-C).

General procedure for hydrolysis of esters

A solution of 1,4-adduct (1 mmol) (obtained from Grignard reactions done in the presence of CuCl), KOH (10 mmol), water (0.5 ml) and ethanol (15 ml) was refluxed for 20 h. Ethanol was then removed from the reaction mixture under vacuum and to the residue thus obtained, was acidified with dil. HCl and then extracted with CH_2Cl_2 repeatedly. The CH_2Cl_2 extracts were mixed together, washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 yielded 3-phenylbutanoic acid (3PBA). The ether layer afforded the precursor alcohol in marginally impure form. No attempt was made to purify further.

Hydrolysis of mixture of 13 and 14

The mixture of **13** and **14** gave 3PBA in 91% yield and **10** in 95% crude yield.

Hydrolysis of mixture of 15 and 16

The mixture of **15** and **16** gave 3PBA in 92% yield and **11** in 96% crude yield.

Hydrolysis of mixture of 17 and 18

The mixture of **17** and **18** gave 3PBA in 88% yield and **12** in 96% crude yield.

Analysis of 3PBA

IR (Neat) ν : 3500-2400 (broad), 1705, 1605, 1585, 1495, 765, 705 cm^{-1}. ^1H NMR (δ) : 1.32 (d, J = 7.0 Hz; 3H, 4-H_3), 2.53-2.71 (m; 2H, 2-H_2), 3.21 (m; 1H, 3-H), 7.17-7.34 (m; 5H, aromatic-H_5).

Analysis of 3PBA obtained from hydrolysis of

Mixture of **13** and **14** : $[\alpha]^{26}_D$ = +12.4(c 9, benzene).
Mixture of **15** and **16** : $[\alpha]^{26}_D$ = -10.2(c 5.44, benzene).
Mixture of **17** and **18** : $[\alpha]^{26}_D$ = +5.6(c 7.13, benzene).

Synthesis of 20 and 21

1,2:5,6-O-acetylidene-α-D-glucofuranose (**19**) (182.2 mg; 0.70 mmol) and 3-phenylbutanoic acid (114.8 mg; 0.70 mmol) were dissolved in dry CH_2Cl_2 (5 ml) and cooled to 0 ^oC. To it, N,N'-dicyclohexylcarbodiimide (186.4 mg; 0.70 mmol) and catalytic amount of N,N'-dimethylaminopyridine were added and the solution stirred for 0.5 h and then further for 1 h at room temperature.[14] The reaction mixture was repeatedly cooled in freezer and filtered to remove insoluble N,N'-dicyclohexylurea. After the removal of solvent from the filtrate, the crude was chromatographed to get **20** and **21** as an inseparable diastereomeric mixture. Yield of the reaction was 255.8 mg (90%).

Analysis of mixture of 20 and 21

IR (KBr) ν : 1740, 1600, 1590, 1490, 765, 710 cm^{-1}. MS : 391 [M^+].

NMR analysis of 20

^{1}H NMR (δ) : 2.62 (d, J = 7.9 Hz; 2-H_2), 3.27 (br. sextet, J = 7.2 Hz; 3-H), 3.83(d, J = 3.7 Hz; 2'-H), 5.13 (d, J = 2.6 Hz; 3'-H), 5.50 (d, J = 3.7 Hz; 1'-H). ^{13}C NMR (δ) : 21.95 (q; 1C, 4-C), 25.17 (q; 1C), 26.02 (q; 1C), 26.57 (q; 1C), 26.73 (q; 1C), 36.41 (d; 1C, 3-C), 42.62 (t; 1C, 2-C), 67.15 (t; 1C, 6'-C), 72.37 (d; 1C), 75.98 (d; 1C), 79.55 (d; 1C), 83.08 (d; 1C), 104.93 (d; 1C, 1'-C), 109.22 (s; 1C, 10'-$C^{\#}$), 111.99 (s; 1C, 7'-$C^{\#}$), 126.54 (d; 2C, 6-C and 10-C), 126.94 (d; 1C, 8-C), 128.50 (d; 2C, 7-C and 9-C), 145.20 (s; 1C, 5-C), 170.62 (s; 1C, 1-C).

NMR analysis of 21

^{1}H NMR (δ) : 3.27 (br. sextet, J = 7.2 Hz; 3-H), 5.16 (d, J = 2.7 Hz; 3'-H), 5.70 (d, J = 3.7 Hz; 1'-H). ^{13}C NMR (δ) : 22.09 (q; 1C, 4-C), 25.17 (q; 1C), 26.02 (q; 1C), 26.57 (q; 1C), 26.73 (q; 1C), 37.28 (d; 1C, 3-C), 42.88 (t; 1C, 2-C), 67.15 (t; 1C, 6'-C), 72.25 (d; 1C), 75.74 (d; 1C), 79.55 (d; 1C), 82.98 (d; 1C), 104.93 (d; 1C, 1'-C), 109.22 (s; 1C, 10'-$C^{\#}$), 111.99 (s; 1C, 7'-$C^{\#}$), 126.62 (d; 2C, 6-C and 10-C), 126.94 (d; 1C, 8-C), 128.42 (d; 2C, 7-C and 9-C), 144.94 (s; 1C, 5-C), 170.98 (s; 1C, 1-C).

Synthesis of 23 and 24

dl-Butan-2-ol (**22**) (48.2 mg; 0.65 mmol) and dl-3-phenylbutanoic acid (107.0 mg; 0.65 mmol) were condensed by the method described above. (S)-butan-2-ol and (S)-3-phenylbutanoic acid were also condensed to distinguish the products from R^*R^* and R^*S^* combinations. The yield of reaction was 131.9 mg (92%).

Analysis of 23 and 24

IR (Neat) ν : 1730, 1605, 1500 cm^{-1}. MS : 220 [M^+].

NMR analysis of 23

^{1}H NMR (δ) : 0.78 (t, J = 7.5 Hz, 4'-H_3), 1.13 (d, J = 6.2 Hz; 1'-H_3), 1.30 (d, J = 7.1 Hz; 4-H_3), 3.27 (br. sextet, J = 7.2 Hz; 3-H), 4.78 (m; 2'-H). ^{13}C NMR (δ) : 9.47 (q; 1C, 4'-C), 19.37 (q; 1C, 1'-C), 21.86 (q; 1C, 4-C), 28.67 (t; 1C, 3'-C), 36.64 (d; 1C, 3-C), 43.28 (t; 1C, 2-C), 72.06 (d; 1C, 2'-C), 126.29 (d; 1C, 8-C), 126.74 (d; 2C, 6-C and 10-C), 128.39 (d; 2C, 7-C and 9-C), 145.73 (s; 1C, 5-C), 171.99 (s; 1C, 1-C).

NMR analysis of 24

^{1}H NMR (δ) : 0.84 (t, J = 7.5 Hz, 4'-H_3), 1.08 (d, J = 6.2 Hz; 1'-H_3), 1.30 (d, J = 7.1 Hz; 4-H_3), 3.27 (br. sextet, J = 7.2 Hz; 3-H), 4.78 (m; 2'-H). ^{13}C NMR (δ) : 9.59 (q; 1C, 4'-C), 19.26 (q; 1C, 1'-C), 21.89 (q; 1C, 4-C), 28.71 (t; 1C, 3'-C), 36.61 (d; 1C, 3-C), 43.21 (t; 1C, 2-C), 72.06 (d; 1C, 2'-C), 126.29 (d; 1C, 8-C), 126.74 (d; 2C, 6-C and 10-C), 128.39 (d; 2C, 7-C and 9-C), 145.73 (s; 1C, 5-C), 172.02 (s; 1C, 1-C).

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