Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

(±) *trans*-3,3'-(1,2-CYCLOPROPANEDIYL)BIS-2-(*E*)-PROPENOIC ACID, DIETHYL ESTER : TANDEM OXIDATION PROCEDURE (TOP) USING MnO₂ OXIDATION-STABILIZED PHOSPHORANE TRAPPING
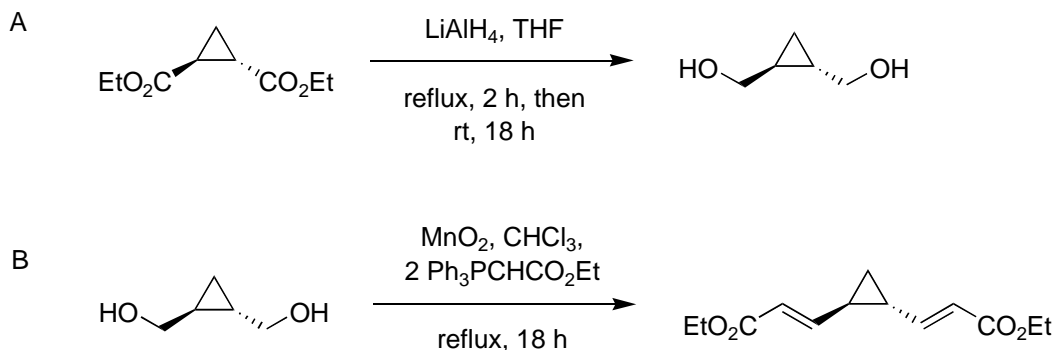
Submitted by Richard J. K. Taylor, Leonie Campbell, and Graeme D. McAllister.[1]

Checked by Robert Webster and Mark Lautens.

1. Procedure

A. *trans 1,2-Bis-(hydroxymethyl)cyclopropane.* (Note 1) A 500-mL, three-necked flask equipped with a Teflon-coated magnetic stirrer, a reflux condenser, a pressure-equalizing dropping funnel, and a gas inlet adaptor attached to a nitrogen line is charged with tetrahydrofuran (100 mL) (Note 2) and lithium aluminium hydride (4.17 g, 109.7 mmol) (Note 3), and the mixture is cooled to 0 ºC (bath temperature) in an ice-water bath. A solution of diethyl *trans*-1,2-cyclopropanedicarboxylate (13.59 g, 73.1 mmol) (Note 4) in THF (25 mL) is added over 1 h via the dropping funnel. After complete addition, the mixture is allowed to warm to room temperature and then is heated to reflux in an oil bath under nitrogen for 2 h. After allowing to cool, it is stirred at room temperature for 18 h. After being cooled in an ice-water bath, the mixture is treated cautiously with sat. aq. NH₄Cl solution (30 mL), whereupon the reaction mixture precipitates granular aluminium salts. Ethyl acetate (30 mL) is added to the mixture and a glass stir rod is used to break up the solid salts and facilitate stirring. The mixture is stirred for 5 h and then is filtered (Note 5). The insoluble salts are re-suspended in ethyl acetate (50 mL) and stirred for 2 h, then filtered again followed by

further washing of the salts with ethyl acetate (2 x 50 mL). The combined filtrates are then dried over Na_2SO_4 (15 g), then are filtered and transferred to a 1-L round-bottomed flask, are evaporated (<40 °C, 8 mmHg) to give 7.45 g of a pale-yellow oil containing the title compound and its mono-acetate derivative in an approximate 3:1 ratio. The crude product is dissolved in methanol (100 mL) and sodium methoxide is added (100 mg) (Note 6). The solvolysis of the acetate can be monitored by TLC and is complete after 3 h at room temperature (Note 7). Neutralization of the mixture using IR-120 acidic ion exchange resin (2 g) (Note 8) followed by filtration and evaporation of the solvent gives 6.81 g (91%) of the crude diol (Note 9), which can be used without purification in the next step.

B. *(±)-Diethyl* trans-*(E,E)-cyclopropane-1,2-acrylate.* A flame-dried, 2-L, one-necked flask equipped with a Teflon-coated magnetic stirrer and a reflux condenser is charged with *trans-1,2-bis*(hydroxymethyl)cyclopropane (5.10 g, 50.0 mmol), manganese(IV) oxide (86.94 g, 1.00 mol) (Note 10), (carbethoxymethylene)triphenylphosphorane (41.81 g, 120.0 mmol) (Note 11), and chloroform (300 mL) (Note 12). The resulting suspension is stirred vigorously with heating in an oil bath to maintain gentle solvent reflux for 18 h. After allowing to cool to room temperature, the suspension is filtered through Celite (Note 13), and is washed with additional chloroform (4 x 100 mL). The filtrate is concentrated under reduced pressure (<40 °C, 8 mmHg), and then diethyl ether (200 mL) is added to the yellow, solid residue. This suspension is stirred at room temperature for 30 min, then the white precipitate (triphenylphosphine oxide) is removed by filtration and is washed with pentane (200 mL) (Note 14). Silica gel (40 g) (Note 15) is added to the combined organic filtrates, and the suspension is concentrated under reduced pressure (<40 °C, 8 mmHg) until the solid is free flowing. This mixture is loaded onto a silica gel column (Note 16) and is eluted with pentane/Et_2O, 3/1 (Note 17). The fractions containing the product (R_f = 0.41; pentane/Et_2O, 2/1) are combined and evaporated under reduced pressure to afford a pale-yellow solid. The solid is dissolved in hot pentane (50 mL) and the solution is allowed to cool to room temperature. The precipitated crystals are collected by suction filtration on a Büchner funnel, then are washed with ice-cold pentane. The crystals are transferred to a 50-mL, round-bottomed flask and are dried at room temperature under high vacuum to provide 7.24 g (61%) of pure diester (Notes 18, 19) as colorless needles. The mother liquors are concentrated under reduced pressure (<40 °C, 8 mmHg), and the yellow residue is purified by chromatography on silica gel

(Note 20), eluting with pentane/diethyl ether, 3/1. The fractions containing the product (R_f = 0.41; pentane/Et$_2$O, 2:1) are combined and evaporated under reduced pressure to afford 1.12 g (9%), total yield, 70%) of the diester.

2. Notes

1.   The preparation of *trans*-1,2-*bis*(hydroxymethyl)cyclopropane was based upon the method of Ashton, *et al.*[2]

2.   Tetrahydrofuran was purchased from Fisher Scientific UK, Ltd, and distilled from sodium/benzophenone prior to use.

3.   Lithium aluminium hydride was purchased from Aldrich Chemical Company, Inc. (reagent grade, 95%, powder, cat. no. 199877) and was used as received.

4.   Diethyl *trans*-1,2-cyclopropanedicarboxylate was purchased from Aldrich Chemical Company, Inc. (97%, cat. no. 157295) and was used as received.

5.   Filtration was performed through use of a 7-cm diameter Büchner funnel (fitted with a 6.5 cm-diameter Fisherbrand QL-100 filter paper) attached to a 500-mL Büchner flask.

6.   Sodium methoxide was purchased from Aldrich Chemical Company, Inc. (powder, 95% cat. no. 164992) and used as received.

7.   (2-(Hydroxymethyl)cyclopropyl)methyl acetate was present as a side product in amounts ranging from 20–30 mol% when using ethyl acetate as an extraction solvent. Extraction yields were improved using this protocol, presumably because of the increased lipophilicity of the side product. The yield decreased when additional water was used during the work-up due to the hydrophilicity of the desired product. It was possible to separate the two compounds using flash chromatography on silica gel with ethyl acetate as an eluent. The methanolysis of the side product[3] proceeded in quantitative yield using the conditions stated in the procedure. The physical properties of the side product were as follows: clear colorless oil; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 0.55 (ddd, 1 H, J = 5.6, 7.2 Hz), 1.07 (m, 2 H), 1.54 (s, 1 H, broad), 2.06 (s, 3 H), 3.47 (dddd, 2 H, J = 11.2, 17.6 Hz), 3.93 (ddd, 2 H, J = 7.2, 11.6, 17.8 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 8.6, 15.9, 20.1, 21.2, 66.2, 68.0, 171.4; IR (film): 3406, 1735 cm^{-1}; LRMS (EI) *m/z* (relative intensity): 145 (MH$^+$) (27%), 127 (100%), 113 (28%), 103

(57%), 84 (36%), 67 (40%), 55 (69%); HRMS [M + H$^+$] calcd for C$_7$H$_{13}$O$_3$: 145.0865. Found: 145.0866

8. Amberlite® IR-120 (plus) ion-exchange resin was purchased from Aldrich Chemical Company, Inc. (cat. no. 216534) and used as received.

9. The crude reduction product was of sufficient purity for direct use in the next step. It can also be purified by bulb-to-bulb distillation in a Kugelrohr apparatus under vacuum (5 mmHg), or alternatively using flash chromatography on silica gel using ethyl acetate as an eluent. The physical properties were as follows: bp 125–128 ℃ / 5 mmHg (Lit.[4] 90 ℃ / 1 mmHg); ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 0.44 (t, 2 H, J = 6.4 Hz), 0.96–1.07 (m, 2 H), 3.07 (dd, 2 H, J = 8.4, 11.2 Hz), 3.70 (s, 2 H, broad), 3.82 (dd, 2 H, J = 4.8, 11.2 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 7.5, 20.2, 66.4; IR (film) cm^{-1}: 3330, 3002, 2873, 1427, 1065, 1024 cm^{-1}; LRMS (EI) m/z (relative intensity): 103 (MH$^+$) (10%), 88 (19%), 86 (75%), 84 (100%), 55 (29%); HRMS [M + H$^+$] calcd for C$_5$H$_{11}$O$_2$: 103.0759. Found: 103.0752.

10. Activated manganese(IV) oxide was purchased from Aldrich Chemical Company, Inc. (cat. no. 217646; <5 μm, activated, 85%). Approximately 10 equivalents per oxidation are typically employed.[5]

11. (Carbethoxymethylene)triphenylphosphorane was purchased from Aldrich Chemical Company, Inc. (cat. no. C510-6) and was used as received.

12. The submitters purchased chloroform from Fisher Scientific UK, Ltd, while the checkers purchased chloroform from Caledon Laboratories Ltd. The solvent was distilled from potassium carbonate prior to use.

13. Filtration was performed through a 2-cm depth of Celite® in a 14-cm diameter Büchner funnel (fitted with a 137.5 mm-diameter Fisherbrand QL-100 filter paper) attached to a 1-L Büchner flask.

14. Pentane (Spectro grade) was purchased by the checkers from Caledon Laboratories Ltd. and used without further purification. The submitters used petroleum ether with a boiling range from 40–60 ℃.

15. 60Å Ultrapure Silica gel (Silicycle) was used by the checkers, while the submitters used Fluka Silica Gel 60 (particle size, 35-70 μm).

16. 60Å Ultrapure Silica gel (Silicycle) (200 g) is placed in a 85 mm-diameter column (70 mm-depth of silica) and eluted with ~1.5-2.5 L of solvent.

17. Thin layer chromatography was carried out using Merck silica gel 60F$_{254}$ pre-coated aluminium foil plates with a thickness of 250 μm, and visualised with UV light (254 nm) and KMnO$_4$ solution.

18. The properties are as follows: mp (uncorr., pentane) 77–79 ℃ (Lit.[6] 73–74 ℃); ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 1.25 (t, 2 H, J = 6.4 Hz, overlapping signal), 1.27 (t, 6 H, J = 7.2 Hz), 1.78–1.84 (m, 2H), 4.17 (q, 4 H, J = 7.2 Hz), 5.89 (d, 2 H, J = 15.5 Hz), 6.45 (dd, 2 H, J = 9.4, 15.5 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ : 14.5, 17.7, 25.4, 60.5, 120.2, 149.7, 166.5; IR (film) cm^{-1}: 2979, 1712, 1645, 1144, 1047; LRMS (EI) m/z (relative intensity): 239 (MH$^+$) (35%), 193 (48%), 164 (44%), 146 (48%), 125 (50%), 119 (62%), 97 (60%), 91 (100%); HRMS [M$^+$] calcd. for C$_{13}$H$_{18}$O$_4$: 238.1205. Found: 238.1209; Anal. Calcd. for C$_{13}$H$_{18}$O$_4$: C, 65.53; H, 7.61; Found: C, 65.59; H,7.94;.

19. The submitters were able to obtain a second crop of crystals, by evaporation of the mother liquor. The solid was dissolved in 20 mL of hot pentane and the solution was cooled to room temperature. Filtration of the crystals and drying as above gave the second crop of diester.

20. 60Å Ultrapure Silica gel (Silicycle) (120 g) was placed in a 50 mm-diameter column (80 mm-depth of silica) and eluted with ~500–600 mL of solvent.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press, Washington, DC, 1995.

3. Discussion

The importance of aldehydes as electrophilic synthetic building blocks cannot be overestimated, but their reactivity can cause difficulties. Aldehydes often undergo aerial oxidation, acid-promoted oligomerisation/polymerisation,[7] or decompose by other means; they can also be difficult to isolate due to their volatility (sometimes with lachrymatory effects) or toxicity.[8] These difficulties can be circumvented by preparing the aldehyde *in situ* and then adding the next reagent to accomplish the carbonyl addition in a one-pot oxidation-trapping process. This sequential approach was first developed by Ireland and Norbeck,[9] who

employed a Swern oxidation followed by the addition of stabilized phosphorane or Grignard reagent to react with the aldehyde formed *in situ*. Similar approaches have been reported more recently by the Ley (TPAP oxidation-Wittig trapping)[10] and Bressette (PCC oxidation-Wittig trapping)[11] groups.

The first truly tandem oxidation-trapping sequence (Dess-Martin periodinane oxidation in the presence of a stabilised phosphorane), was reported by Huang in 1987,[12] with the scope of the process being expanded by Barrett *et al*. in 1997.[13] More recently, Matsuda's group have reported the use of barium permanganate for similar one-pot reactions.[14] Crich and Mo subsequently used IBX as an *in situ* oxidant with a stabilized Wittig reagent for the preparation of several 2'-deoxynucleosides[15] and more recently, Maiti and Yadav demonstrated that this IBX procedure can be employed with a range of activated and non-activated alcohols.[16]

The York group have developed a range of one-pot "tandem oxidation processes" (TOP) utilizing activated manganese(IV) oxide in combination with a variety of nucleophilic trapping agents (including phosphoranes, phosphonates, sulfuranes, amines and alcohols), and many of these procedures have found applications in the wider chemical community.[5] The low toxicity, low cost and ease of handling of activated MnO_2, combined with its commercial availability and the absence of hazardous additives/by-products, are attractive. The heterogeneous nature of the oxidant means that the work-up consists of simple filtration followed by evaporation of solvent. Although an excess of oxidant is usually required (Note 2), the spent oxidant can be reactivated/recycled.[5,17]

The manganese(IV) oxide TOP-Wittig methodology has been applied to a range of "activated" alcohols (allylic, propargylic and benzylic examples) as shown in Table 1, with the successful homologation of *Z*-allylic alcohols (*e.g.* entries 3-6) with complete retention of the pre-existing alkene geometry particularly noteworthy.[18] More surprisingly, however, is that MnO_2 (in the presence of stabilized phosphoranes) has been shown to be an efficient oxidant of "semi-" and unactivated alcohols to afford unsaturated esters in good yield (Table 2).[19]

The procedure described herein is a one-pot process for the preparation of (±)-diethyl *trans* (*E,E*)-cyclopropane-1,2-acrylate from *trans*-cyclopropane-1,2-methanol, using a MnO_2 oxidation-stabilised phosphorane olefination sequence. The process is straightforward and herein is carried

20

out on a 50-mmol scale (which could presumably be scaled up further).

Table 1 – The One-Pot Procedure using Activated Alcohols[17]
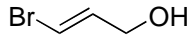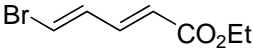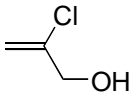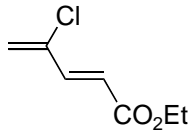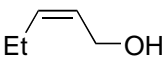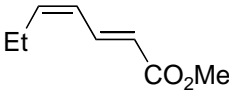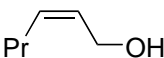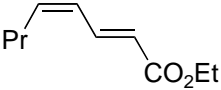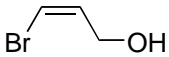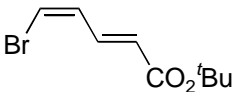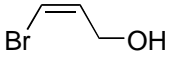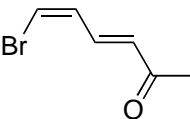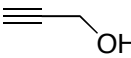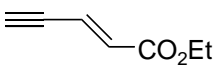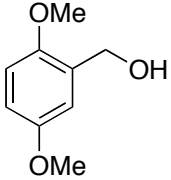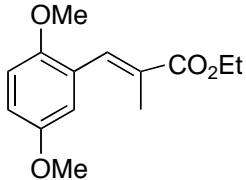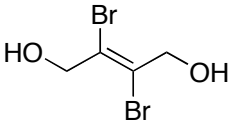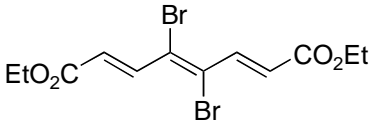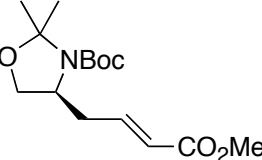
Entry	Substrate	Product	Yield (%)
1	Br⎼⎼⎼OH	Br⎼⎼⎼CO₂Et	81 (E,E:E,Z:Z,E:Z,Z = 18:6:3:1)
2	Cl / OH	Cl / CO₂Et	51 (E,Z = 9:1)
3	Et / OH	Et / CO₂Me	81 (E,Z;Z,Z = 9:1)
4	Pr / OH	Pr / CO₂Et	81 (E,Z;Z,Z = 9:1)
5	Br / OH	Br / CO₂ᵗBu	90 (E,Z;Z,Z = 5:1)
6	Br / OH	Br / =O	73 (E,Z;Z,Z = 8:1)
7	≡ / OH	≡ / CO₂Et	82 (E,Z = 4:1)
8	OMe / OH / OMe	OMe / CO₂Et / OMe	80 (>98%E)
9	Br, HO / OH, Br	Br, EtO₂C / CO₂Et, Br	84 (>98% E,E,E)

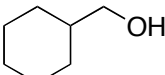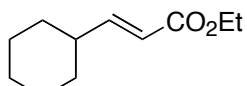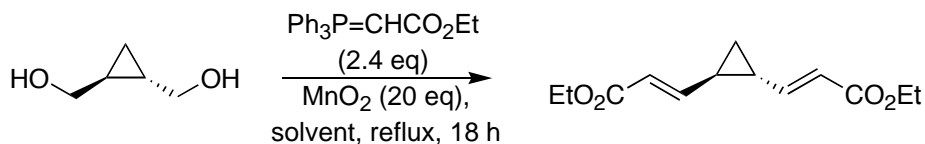**Table 2** – The One-Pot Procedure using "Semi-Activated" and Unactivated Alcohols[18]
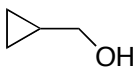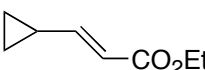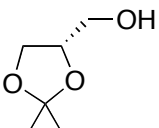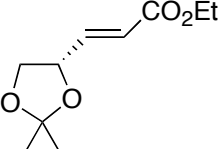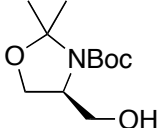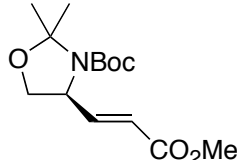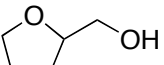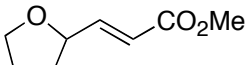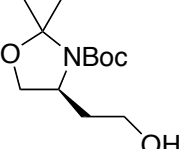
Entry	Substrate	Product	Yield (%)
1			86 (>99% *E*)
2			74 (*E,Z* = 3:1)
3			58 (>98% *E*)
4			66 (*E,Z* = 6:1)
5			70 (>95% *E*)
6	C_9H_{19}—OH	C_9H_{19}—CO$_2$Et	80 (>95% *E*)
7	C_5H_{11}—OH	C_5H_{11}—CO$_2$Et	70 (>95% *E*)
8	Ph—OH	Ph—CO$_2$Et	86 (>95% *E*)
9			51 (>99% *E*)
10	C_9H_{19}—OH	C_9H_{19}—CON(OMe)Me	57 (*E:Z* = 11.5:1)

Table 3 – Optimization of the Synthesis

Entry	Solvent / time	Yield (%)
1	CHCl$_3$ / 18 h	72–75
2	THF / 18 h	45
3	Toluene / 18 h	35[a]

[a] The low yield may be attributed to volatility of the intermediate aldehyde

Table 3 shows the results of the optimisation of this reaction with regards the choice of solvent. The best conditions involve 10 eq. of MnO$_2$ and 1.2 eq. of phosphorane per oxidation, with chloroform as the solvent of choice.

Diethyl *trans* (*E*,*E*)-cyclopropane-1,2-acrylate has been reported several times in the literature, in each case by an oxidation-olefination sequence. McDonald, Verbicky and Zercher[6] reported the oxidation (by TPAP/NMO) of (*E*)-cyclopropane-1,2-methanol, followed by Horner-Wadsworth-Emmons olefination of the isolated dialdehyde. In 1996, Barrett *et al.*[20] reported the synthesis by a one-pot Dess-Martin oxidation-Wittig sequence in their approach to the transfer protein inhibitor U-106305.

In summary, the procedure presented here is an illustration of the one-pot TOP-Wittig trapping route from simple alcohols to α,β-unsaturated carbonyl compounds using MnO$_2$ as the oxidant. This procedure is operationally straightforward, and results in a reduced number of steps, giving significant time-cost benefits.

1. Department of Chemistry, University of York, Heslington, York YO10 5DD, UK.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Diethyl *trans*-1,2-cyclopropanedicarboxylate; (3999-55-1)

Bis-(Hydroxymethyl)-cyclopropane; (2345-75-7)

(±)-Diethyl (*E,E,E*)-cyclopropane-1,2-acrylate

Manganese(IV) oxide; (1313-13-9)

(Carbethoxymethylene)triphenylphosphorane; (1099-45-2)

2-Propenoic acid, 3,3'-(1,2-cyclopropanediyl)bis-, diethyl ester, [1**α**(E),2**β**(E)]-; (58273-88-4)

Richard Taylor obtained BSc and PhD (Dr. D. Neville Jones) from the University of Sheffield. Postdoctoral periods with Dr. Ian Harrison (Syntex, California) and Professor Franz Sondheimer (University College London) were followed by lectureships at the Open University and then UEA, Norwich. In 1993 he moved to a Chair at the University of York. Taylor's research interests centre on the synthesis of bioactive natural products and the development of new synthetic methodology. His awards include the Royal Society of Chemistry's Pedlar Lectureship (2007). Taylor is the immediate past-President of the RSC Organic Division and an Editor of Tetrahedron.

Leonie Campbell (nee Blackburn) was born in Leigh, Lancashire in 1975. Her undergraduate studies were undertaken at Oxford University where she received a M.Sc. (Hons) in 1998. She then moved to the University of York to join the research group of Professor Taylor for her D. Phil. working on tandem in situ oxidation-homologation procedures and their utilisation in natural product syntheses. She is currently working at AstraZeneca (Alderley Park) as a Senior Research Scientist in Medicinal Chemistry.

Graeme McAllister was born in Bellshill, Scotland in 1974. His undergraduate studies were carried out at the University of Glasgow, where he received his B.Sc. (Hons.) in 1996. He stayed at the University of Glasgow to join the research group of Richard C. Hartley, conducting research into the total synthesis of chalcomoracin, and the identification/isolation of a Diels-Alderase enzyme. In 1999, he joined the research group of Professor Taylor at the University of York, initially as a postdoctoral researcher and latterly as experimental officer, where he has carried out research, primarily into novel applications of the Ramberg-Bäcklund reaction, as well as developing new one-pot tandem methodology processes and investigating natural product syntheses.

Rob Webster was born in 1981 in Saskatoon, Saskatchewan, Canada. He obtained his BSc. from the University of Saskatchewan in 2004. During this time he had the opportunity to work in the research labs of Prof. Marek Majewski; and at both Merck-Frosst Canada Ltd. in process research under the supervision of Dr. Francis Gosselin and at Boehringer-Ingelheim Canada Ltd. in combinatorial chemistry working under Dr. Jean Rancourt and Sophie Goulet. He began his Ph.D. work in 2004 at the University of Toronto in the lab of Prof. Mark Lautens, where he is currently, in the area of natural product total synthesis and asymmetric catalysis.
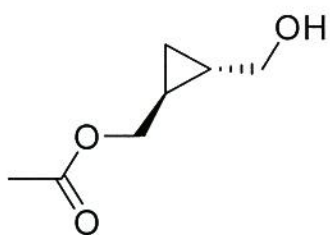
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0.516

0.550   0.500

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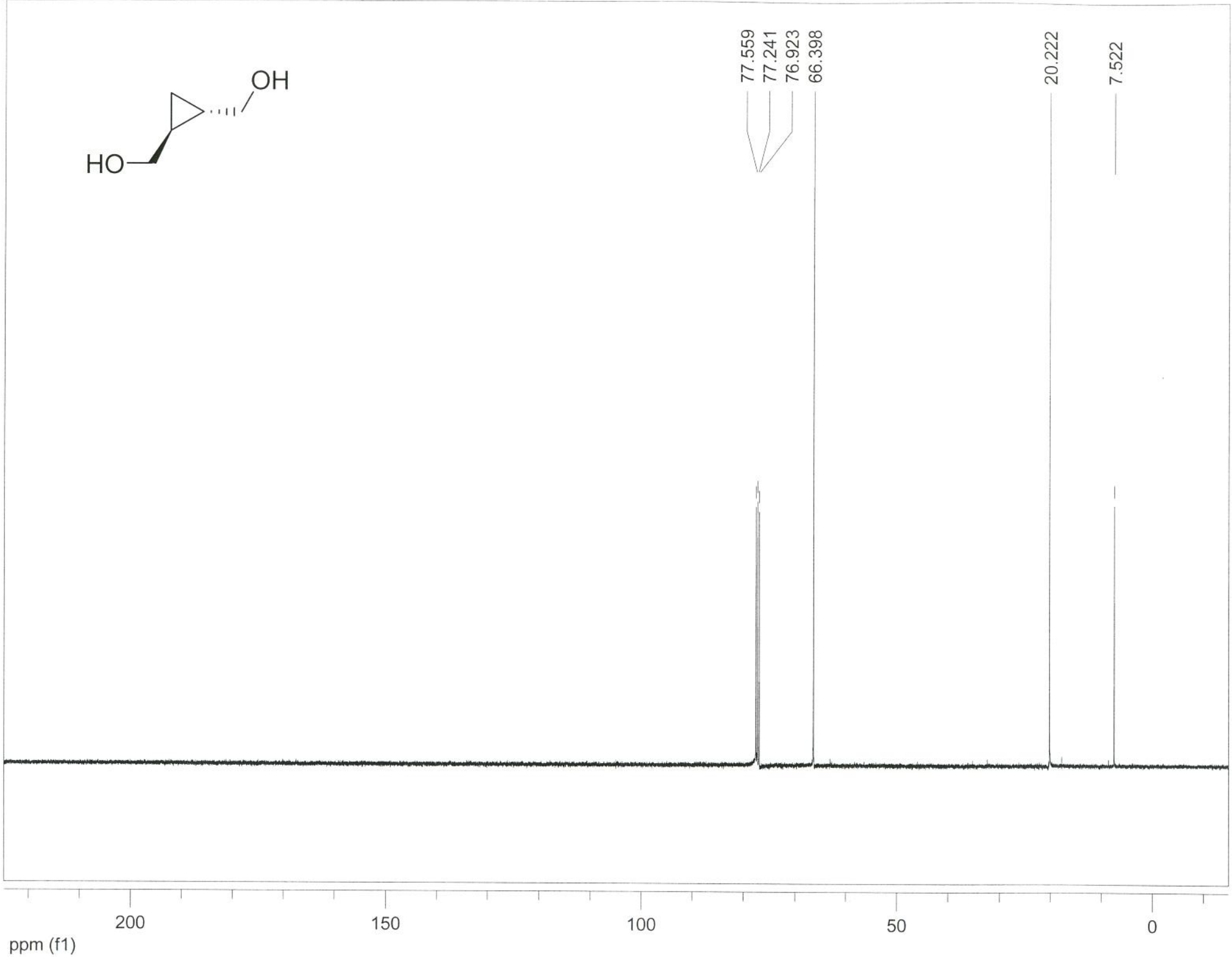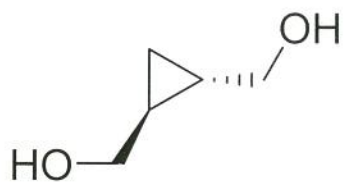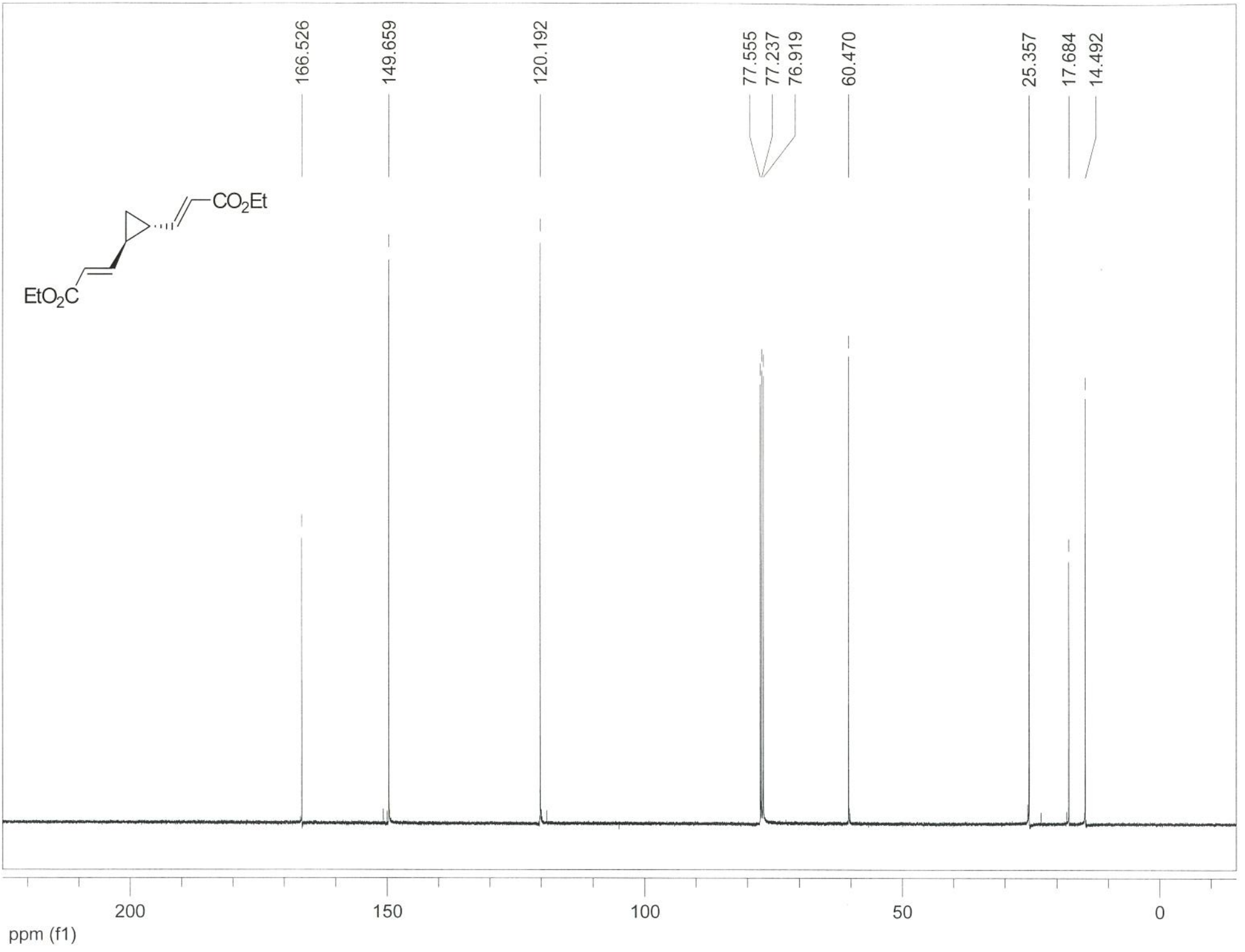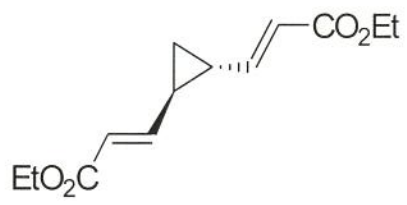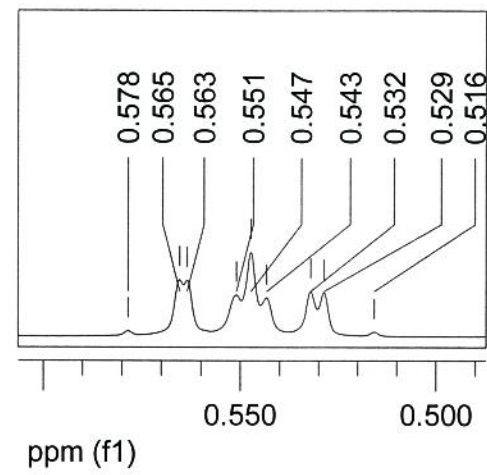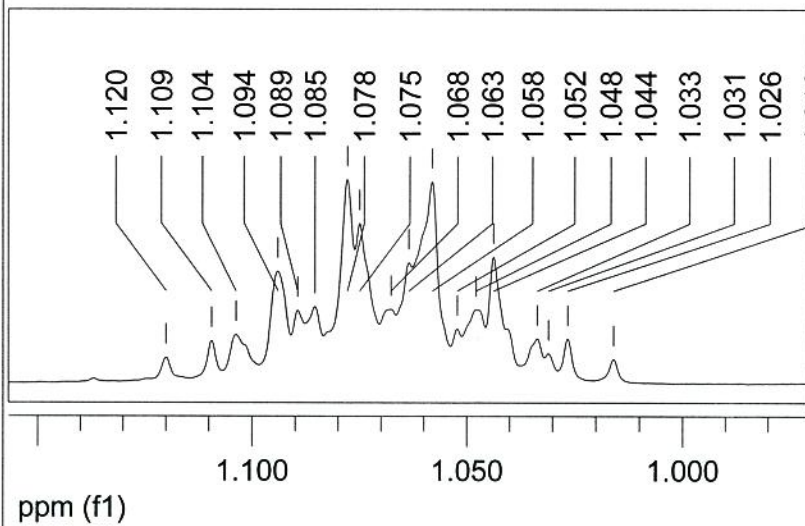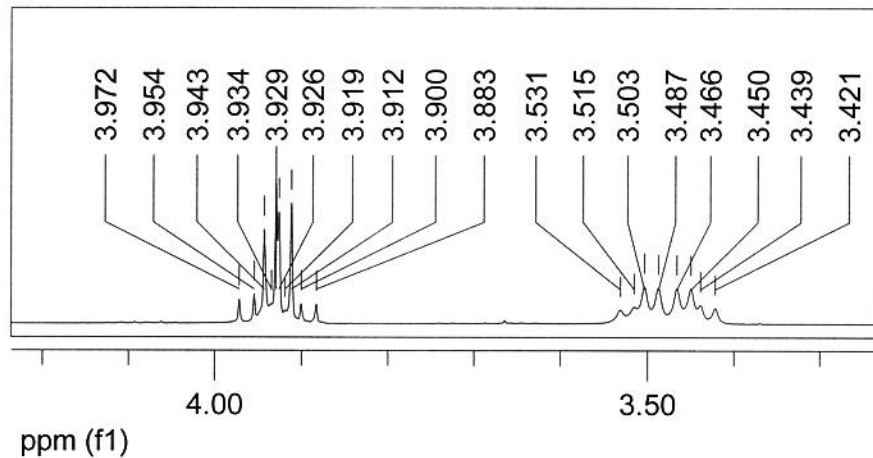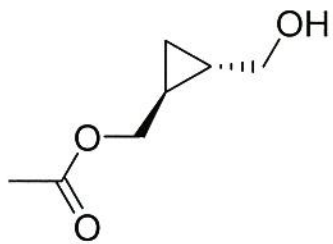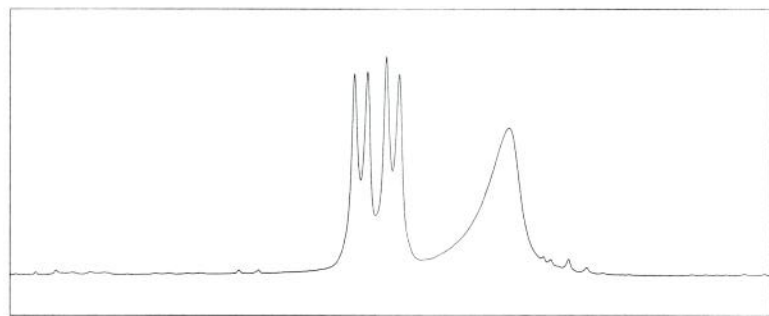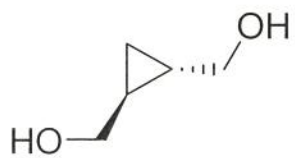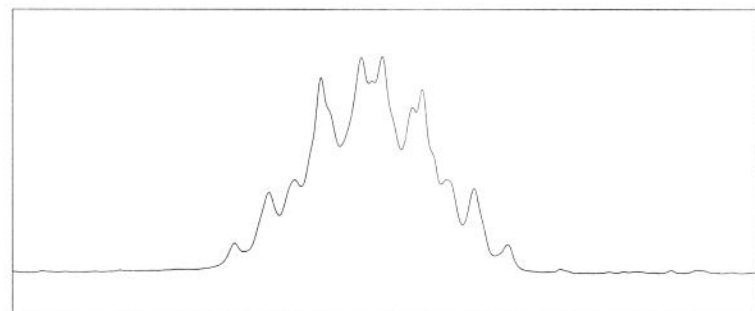
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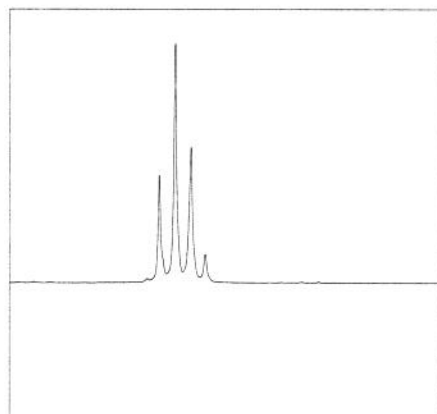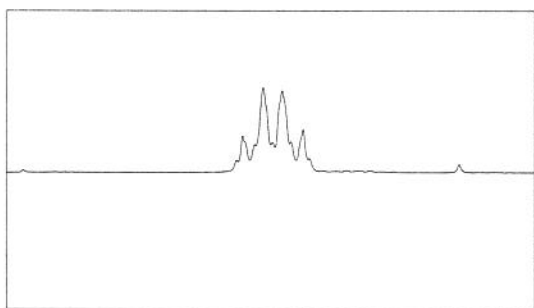1.234
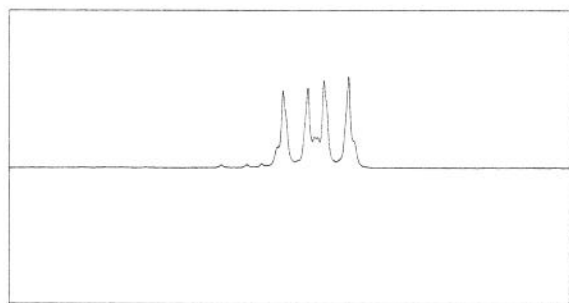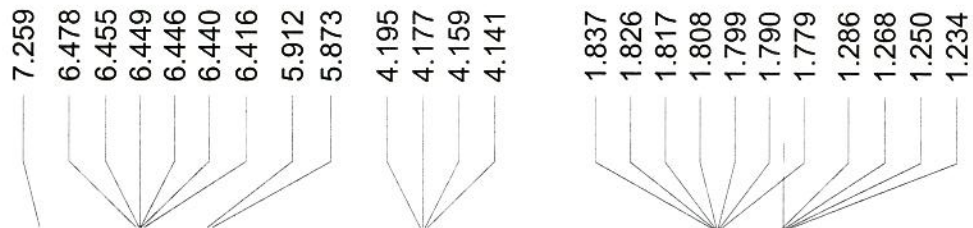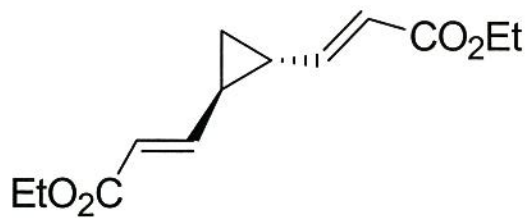
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ppm (f1)

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ppm (f1)

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1.90
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2.02
7.81

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ppm (f1)