

Diastereoselective 1,3-dipolar cycloaddition of pyrylium ylides with chiral enamides†

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Chiral enamides **5f–i** were found to react with pyrylium ylides to give cycloadducts **6d–i** in good yields with an excellent level of stereoselectivity. The chiral auxiliary was successfully removed on hydrogenolysis of compound **6f** in continuous flow (H-Cube) resulting in the first asymmetric synthesis of complex amine **8**.

Introduction

1,3-Dipolar cycloaddition of pyrylium ylides **1** with activated alkenes is a powerful synthetic tool providing direct access to the 8-oxa-bicyclo[3,2,1]octane motif **2** (Fig. 1).^{1–3} Common in a number of biologically active natural products such as englerin A^{4,5} **3** and aspergillin PZ,⁶ the oxygen bridged bicycle **2** has potential as a scaffold for the development of pharmaceuticals.

Our group became involved in finding new applications for this interesting reaction,⁷ with particular attention drawn to the discovery of new polarophiles and reaction conditions. Indeed, the use of nitrogen as an alkene activator will allow direct synthesis of the bicyclic amine **2** (X = NH₂). Therefore it is proposed that attachment of chiral auxiliaries on the nitrogen will allow a stereoselective 1,3-dipolar cycloaddition. Only one example of a diastereoselective 1,3-dipolar cycloaddition of pyrylium ylides with chiral acrylic esters was reported by Chen and Nicolaou in their total synthesis of englerin A.⁵ For this study it was decided to investigate chiral enamides, which were success-

fully applied as polarophiles in a number of cycloaddition reactions by Hsung and co-workers.⁸

Results and discussion

All starting materials for this study were prepared according to literature procedures. Acetoxy pyrones **4a–c** were prepared from corresponding furyl alcohols⁹ or fructose.¹⁰ Enamides **5a**, **5f** and **5g** were prepared *via* palladium catalysed *trans*-vinylation;¹¹ ynamide **5e** and enamides **5b–d** and **5h** were prepared by copper catalysed cross-couplings.¹²

At first we decided to establish the best cycloaddition conditions for reactions with non-chiral enamides (Table 1). Acetoxy pyrone **4a** was reacted under triethyl amine promoted conditions (A)² and thermal conditions (B).¹

Under both sets of conditions the reactions with the simplest enamide **5a** proceeded smoothly to give the desired product **6a**. The yield was marginally better under thermal conditions, although this reaction required a significantly longer time to reach complete conversion of the starting material. The slightly lower yield of the base-promoted reaction was due to formation of the pyrylium ylide dimer **7**² as a minor byproduct. Reaction of the *trans*-enamide **5b** produced the product **6b** but in a lower yield, while the *cis*-enamide **5c** gave no detectable cycloaddition. Cycloaddition of the *gem*-disubstituted alkene **5d** gave a different product, which decomposed upon attempts at purification by column chromatography. Our tentative assignment of the structure **6c** was made on the basis of the crude ¹H NMR analysis, which showed the absence of the enone double bond, and instead the presence of resonances corresponding to the double bond of the cyclic enol ether. Formation of this regioisomer is unusual and will be further investigated in a separate study.

The ynamide **5e** gave no cycloaddition products under either thermal or base catalysed conditions.

Having established that the mono-substituted double bond gave the best yields of the cycloadduct, we proceeded to

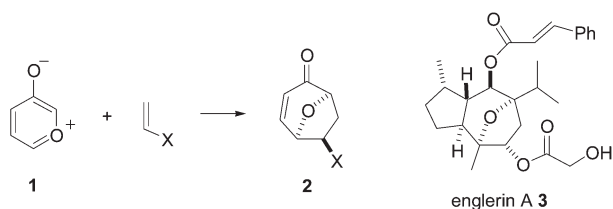
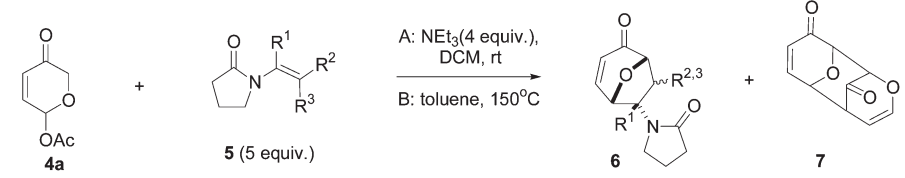
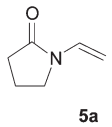
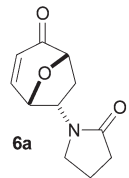
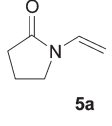
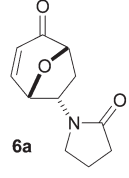
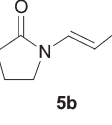
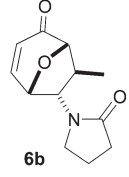
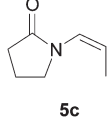
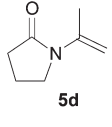
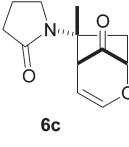
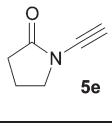


Fig. 1 1,3-Dipolar cycloaddition approach to 8-oxa-bicyclo[3,2,1]-octanes.

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† Electronic supplementary information (ESI) available: ¹H and ¹³C spectra for cycloadducts **6a–i** and acetamide **8**. CCDC reference number 856583. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob07007c

Table 1 Cycloadditions with simple enamides **5a–e**

Enamide	Conditions	Time (d)	Product	Yield
				
 5a	A	1.5	 6a	72%
 5a	B	4	 6a	85%
 5b	A	2	 6b	32%
 5c	A	2	—	—
 5d	A	1.5	 6c	ca. 25% (decomposed on purification)
 5e	A or B	2	—	—

investigate the reactions of chiral enamides **5f–h** under base promoted milder reaction conditions (Table 2).

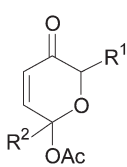
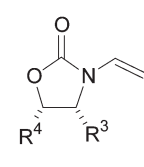
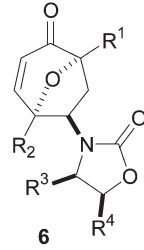
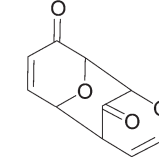
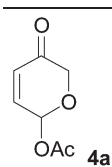
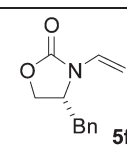
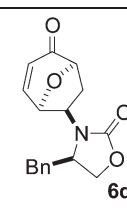
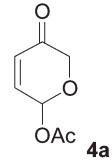
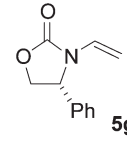
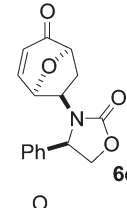
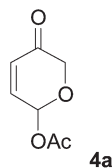
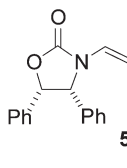
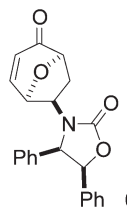
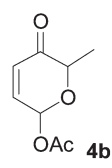
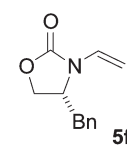
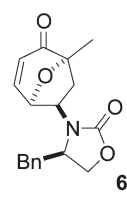
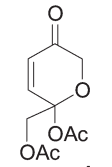
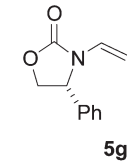
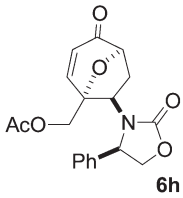
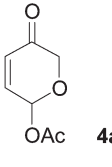
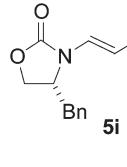
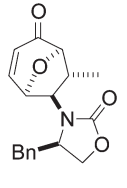
Gratifyingly, cycloaddition reactions of terminal enamides **5f–h** proceeded in moderate to good yields and the products were formed as single diastereoisomers. Chiral *trans*-enamide **5i** gave cycloadduct **6i** in a lower yield as was expected from our initial experiments. The relative stereochemistry of the cycloadducts was established *via* X-ray analysis of **6d** (Fig. 2) and further correlation of the NMR data for the products.

The stereochemical outcome of the reactions can be rationalized by the model presented in Fig. 3. The enamide assumes the

preferred conformation⁸ and the *endo* cycloaddition¹³ happens on the least hindered face of the alkene giving rise to the observed stereochemistry of the adducts.

To conclude this study we decided to demonstrate possible cleavage of the chiral auxiliary. Cycloadduct **6f** was reduced on a continuous flow hydrogenation setup (H-Cube) to give both reduction of the enone double bond and cleavage of the chiral auxiliary. We discovered that direct purification of the primary amine by column chromatography was problematic due to its high polarity and the crude product was converted into an acetamide **8**, which was isolated in a 50% yield after two steps (Scheme 1).

Table 2 Cycloadditions with chiral enamides **5f-i**

Pyrone	Enamide	Temp	Time (h)	Product	Yield (%)
		NEt_3 (4 equiv.), DCM, temp.			
		rt	24		59
		rt	48		45
		rt	48		51
		50 °C	48		63
		rt	24		87
		rt	48		21

Conclusions

In summary, we have demonstrated the first example of the use of amides as alkene activators in the 1,3-dipolar cycloaddition

reactions of pyrylium ylides. The use of chiral oxazolidinones as chiral auxiliaries leads to highly stereoselective cycloadditions and the first asymmetric synthesis of the bicyclic amine **8**.

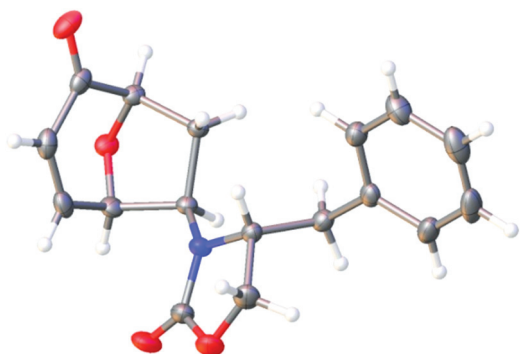


Fig. 2 Ortep plot of the X-ray structure of 6d.

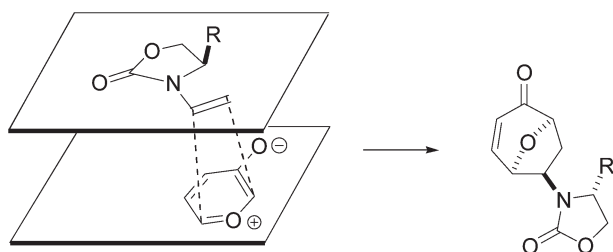
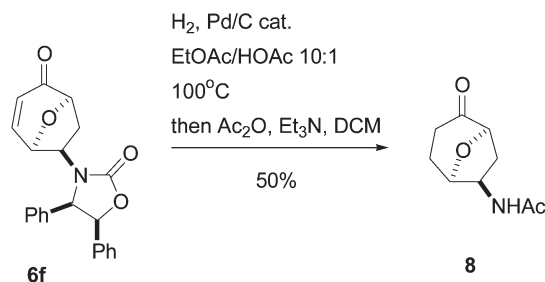


Fig. 3 Cycloaddition model.



Scheme 1 Cleavage of the chiral auxiliary.

Experimental section

All reactions were carried out under an inert atmosphere (N_2) unless stated otherwise. Reaction solvents (toluene, CH_2Cl_2) were freshly distilled from calcium hydride under a N_2 atmosphere prior to use. All NMR spectral data was collected on Bruker DRX-500 or Bruker AV-400 spectrometers. IR spectra were collected on a Perkin-Elmer Spectrum One FT-IR spectrometer, optical rotations were measured on a Perkin-Elmer Model 341 polarimeter and mass-spec data was collected on a Waters GCT-Premier spectrometer with NanoMate attachment.

Base promoted cycloadditions (method A)

To a stirred solution of acetoxy pyrones **4** (1.28 mmol) and enamides **5** (6.4 mmol) in DCM (5 mL) was added triethylamine (696 μ L, 5.12 mmol) in three equal portions over a period of 36 h at room temperature. Stirring was continued for another

12 h when TLC analysis indicated complete consumption of the starting material **4**. Solvents and volatiles were removed under reduced pressure and the residue was purified by column chromatography (40–60 petroleum ether–ethyl acetate 3 : 1) to give the cycloadducts **6**.

Thermal cycloadditions (method B)

A solution of acetoxy pyrones **4** (1.28 mmol) and enamides **5** (6.4 mmol) in toluene (7 mL) was placed in a sealed tube containing a Teflon stirrer bar. The sealed tube was flushed with N_2 , sealed with a Teflon screw-cap and heated in an oil bath (150 $^{\circ}C$) under stirring until TLC indicated complete consumption of the starting material **4** (usually after a period of 4 days). The reaction mixture was allowed to cool down, volatiles were removed under reduced pressure and the residue was purified by column chromatography (40–60 petroleum ether–ethyl acetate 3 : 1) to give the cycloadducts **6**.

Cycloadduct 6a a white solid: m.p. 76 $^{\circ}C$; $\lambda_{max}(KBr)$ 1740 (m), 1686 (s); m/z (ES^+) found 208.0974 (MH^+) $C_{11}H_{14}NO_3$ requires 208.0974; 1H (500 MHz, $CDCl_3$) δ 1.82 (1H, ddd, J 14.0, 6.0, 1.5 Hz), 2.04 (2H, m), 2.40 (2H, t, J 8.5 Hz), 2.67 (1H, ddd, J 14.0, 9.0, 6.0 Hz), 3.28 (2H, m), 4.56 (1H, d, J 9.0 Hz), 4.70 (1H, dt, J 10.0, 6.0 Hz), 5.40 (1H, dd, J 6.0, 4.5 Hz), 6.15 (1H, dd, J 10.0, 1.5 Hz), 7.22 (1H, dd, J 10.0, 4.5 Hz). ^{13}C (125 MHz, $CDCl_3$) 0.0, 8.7, 12.6, 28.2, 36.4, 55.1, 62.1, 105.9, 132.5, 157.8, 177.9.

Cycloadduct 6b a white solid: m.p. 90–91 $^{\circ}C$; $\lambda_{max}(KBr)$ 1752 (s), 1697 (m); m/z (ES^+) found 221.1121 (MH^+) $C_{12}H_{16}NO_3$ requires 221.1130; 1H (500 MHz, $CDCl_3$) δ 1.38 (3H, d, J 6.0 Hz), 2.01 (2H, m), 2.27 (1H, m), 2.41 (2H, t, J 9.0), 3.29 (2H, m), 4.13 (1H, s), 4.23 (1H, app t, J 6.0 Hz), 5.13 (1H, dd, J 6.0, 5.0 Hz), 6.11 (1H, dd, J 10.0, 1.5 Hz), 7.21 (1H, dd, J 10.0, 5.0 Hz). ^{13}C (125 MHz, $CDCl_3$) 0.0, 0.9, 12.6, 17.5, 28.2, 44.7, 56.3, 69.2, 109.2, 132.5, 157.8, 177.5.

Cycloadduct 6d a white solid: m.p. 131 $^{\circ}C$; $[\alpha]_D^{20} = +370.1$ ($c = 0.95$, $CHCl_3$); $\lambda_{max}(KBr)$ 1750 (s), 1696 (s); m/z (ES^+) found 300.1236 (MH^+) $C_{17}H_{18}NO_4$ requires 300.1236; 1H (500 MHz, $CDCl_3$) δ 1.80 (1H, dd, J 13.5, 1.5 Hz), 2.70 (2H, m), 3.10 (1H, dd, J 13.5, 4.0 Hz), 3.88 (1H, ddd, J 14.0, 9.0, 8.5 Hz), 4.09 (1H, app s), 4.10 (1H, app s), 4.20 (1H, ddd, J 10.0, 6.0, 4.5 Hz), 4.50 (1H, dd, J 8.5, 1.5 Hz), 5.50 (1H, dd, J 6.0, 4.5 Hz), 6.10 (1H, dd, J 10.0, 1.5 Hz), 7.10 (1H, d, J 10.0 Hz), 7.3 (5H, m); ^{13}C (125 MHz, $CDCl_3$) 29.7, 37.9, 55.7, 58.9, 66.6; 74.9, 80.2, 127.5, 127.7, 129.1, 129.2, 135.1, 151.1, 157.7, 196.4.

Cycloadduct 6e a white solid; m.p. 168–170 $^{\circ}C$; $[\alpha]_D^{20} = +8.8$ ($c = 1.0$, $CHCl_3$); $\lambda_{max}(KBr)$ 1755 (s), 1708 (s), 1409 (s); m/z (ES^+) found 286.1089 (MH^+) $C_{16}H_{16}NO_4$ requires 286.1079; 1H (400 MHz, $CDCl_3$) δ 1.68 (1H, dd, J 13.5, 1.5 Hz), 2.28 (1H, ddd, J 13.5, 10.0, 8.5 Hz), 4.02 (1H, ddd, J 10.0, 8.5, 4.5 Hz), 4.21 (1H, dd, J 8.5, 3.0 Hz), 4.38 (1H, dd, J 8.0, 1.5 Hz), 4.61 (1H, dd, J 8.5, 8.5 Hz), 4.68 (1H, dd, J 8.5, 3.0 Hz), 5.36 (1H, dd, J 6.0, 4.5), 6.17 (1H, dd, J 10.0, 1.5 Hz), 7.20–7.45 (6H, m). ^{13}C (125 MHz, $CDCl_3$) 29.3, 56.0, 61.5, 70.4, 74.5, 80.1, 126.2, 127.9, 129.5, 129.7, 138.3, 150.9, 158.3, 190.4.

Cycloadduct 6f a white solid; m.p. 195–199 $^{\circ}C$; $[\alpha]_D^{20} = +25.9$ ($c = 2.8$, $CHCl_3$); $\lambda_{max}(KBr)$ 1742 (s), 1685 (s), 1400 (s); m/z (ES^+) found 384.1230 (MNa^+) $C_{22}H_{19}NO_4Na$ requires

384.1212; ^1H (400 MHz, CDCl_3) δ 1.65 (1H, dd, J 13.5, 2.0 MHz), 2.26 (1H, ddd, J 13.5, 9.5, 8.5 Hz), 4.20 (1H, ddd, J 10.0, 9.5, 6.0 Hz), 4.40 (1H, dd, J 8.5, 1.5 Hz), 4.86 (1H, d, J 7.0 Hz), 5.48 (1H, dd, J 6.0, 4.5 Hz), 5.82 (1H, d, J 7.0 Hz), 6.23 (1H, dd, J 10.0, 1.5 Hz), 5.95–7.16 (10H, m), 7.46 (1H, dd, J 10.0, 4.5 Hz). ^{13}C (125 MHz, CDCl_3) 12.1, 38.8, 49.6, 57.1, 62.7, 63.0, 108.3, 110.3, 110.5, 110.6, 111.2, 11.3, 115.7, 115.8, 139.5, 178.8.

Cycloadduct 6g a white solid; m.p. 136–138 °C; $[\alpha]_{\text{D}}^{20} = -267$ ($c = 0.4$, CHCl_3); $\lambda_{\text{max}}(\text{KBr})$ 1755 (s), 1721 (m); m/z (ES^+) found 336.1221 (MNa^+) $\text{C}_{18}\text{H}_{19}\text{NO}_4\text{Na}$ requires 336.1212; ^1H (500 MHz, CDCl_3) δ 1.51 (3H, s), 1.98 (1H, dd, J 12.0, 6.5 Hz), 2.26 (1H, dd, J 12.0, 9.0 Hz), 2.70 (1H, dd, J 13.5, 10.0 Hz), 3.06 (1H, dd, J 13.5, 4.0 Hz), 3.84 (1H, app t, J 5.0 Hz), 4.10 (2H, app d, J 5.0 Hz), 4.32 (1H, ddd, J 9.0, 6.5, 6.0 Hz), 6.41 (1H, dd, J 6.0, 5.0 Hz), 6.13 (1H, d, J 9.5 Hz), 7.10–7.33 (6H, m). ^{13}C (125 MHz, CDCl_3) 18.5, 35.2, 36.8, 55.0, 57.7, 64.5, 74.5, 83.0, 126.4, 128.1, 128.2, 134.1, 149.8, 156.6, 196.8.

Cycloadduct 6h a white solid; m.p. 138–140 °C; $[\alpha]_{\text{D}}^{20} = +110.5$ ($c = 1.0$, CHCl_3); $\lambda_{\text{max}}(\text{KBr})$ 1776 (m), 1720 (s), 1680 (m), 1257 (s); 1240 (s); m/z (ES^+) found 380.1068 (MNa^+) $\text{C}_{19}\text{H}_{19}\text{NO}_6\text{Na}$ requires 380.1110; ^1H (500 MHz, CDCl_3) δ 1.55 (1H, ddd, J 13.5, 6.0, 1.5 Hz), 2.11 (3H, s), 2.36 (1H, ddd, J 13.5, 10.0, 8.5 Hz), 4.10 (1H, dd, J 8.5, 2.5 Hz), 4.34 (1H, d, J 13.0 Hz), 4.40 (1H, dd, J 8.5, 1.5 Hz), 4.54 (1H, app t, J 8.5 Hz), 4.61 (1H, dd, J 10.0, 6.0 Hz), 4.65 (1H, dd, J 8.5, 2.5 Hz), 4.72 (1H, d, J 13.0 Hz), 6.30 (1H, dd, J 10.0, 1.5 Hz), 7.10–7.40 (6H, m). ^{13}C (125 MHz, CDCl_3) 3.11, 11.2, 39.9, 42.0, 47.4, 52.9, 62.4, 64.8, 108.0, 111.7, 111.9, 115.5, 121.9, 132.1, 140.6, 152.8, 177.6.

Cycloadduct 6i a pale grey viscous oil; $[\alpha]_{\text{D}}^{20} = -220$ ($c = 0.3$, CHCl_3); $\lambda_{\text{max}}(\text{thin film})$ 1748 (s), 1693 (s), 1412 (m), 736 (m); m/z (ES^+) found 314.1366 (MH^+) $\text{C}_{18}\text{H}_{20}\text{NO}_4$ requires 314.1392; ^1H (500 MHz, CDCl_3) δ 1.55 (1H, ddd, J 13.5, 6.0, 1.5 Hz), 2.11 (3H, s), 2.36 (1H, ddd, J 13.5, 10.0, 8.5 Hz), 4.10 (1H, dd, J 8.5, 2.5 Hz), 4.10 (1H, dd, J 8.5, 2.5 Hz), 2.38 (1H, m), 2.62 (1H, dd, J 13.5, 10.5 Hz), 3.06 (1H, dd, J 13.5, 3.5 Hz), 3.78 (1H, m), 3.92 (1H, dd, J 6.0, 4.5 Hz), 3.96 (1H, dd, J 6.5, 1.0 Hz), 4.01 (1H, dd, J 6.0, 1.5 Hz), 4.11 (1H, s), 5.34 (1H, dd, J 6.5, 4.0 Hz), 6.06 (1H, d, J 9.5 Hz), 7.03–7.30 (6H, m); ^{13}C (125 MHz, CDCl_3) 20.7, 37.3, 38.4, 58.4, 64.1, 66.6, 76.2, 88.4, 127.6, 127.7, 129.1, 129.2, 134.9, 151.7, 157.5, 196.0.

Acetamide 8

A solution of cycloadduct **6f** (68 mg, 0.19 mmol) in EtOAc–AcOH (10 : 1, 5 mL) was continuously passed through a Pd/C cartridge at 80 °C on the H-Cube hydrogenation setup working

in full hydrogenation mode until TLC indicated disappearance of compounds running mid-plate in hexane–EtOAc 2 : 1 mixture. Solvents were removed under vacuum and to the residual ammonium acetate salt was added DCM (10 mL), Et_3N (0.5 mL, excess) and acetic anhydride (0.2 mL, excess). The resulting mixture was stirred for 6 h and concentrated. The residue was purified by flash column chromatography (40–60 petrol–EtOAc 3 : 1) to give the product **8** (17.4 mg, 50%) as a colourless oil: $[\alpha]_{\text{D}}^{20} = +115.5$ ($c = 1.01$, CHCl_3); $\lambda_{\text{max}}(\text{thin film})$ 3490 (br m), 2950 (m), 1720 (s), 1650 (s); m/z (ES^+) found 184.0981 (MH^+) $\text{C}_9\text{H}_{14}\text{NO}_3$ requires 184.0974; ^1H (500 MHz, CDCl_3) δ 1.68 (1H, dd, J 14.0, 1.5 Hz), 2.09 (3H, s), 2.13 (1H, m), 2.28 (1H, dd, J 13.0, 7.5 Hz), 2.41 (1H, dd, J 17.0, 8.0 Hz), 2.58–2.76 (2H, m), 4.20 (1H, d, J 8.0 Hz), 4.44 (1H, app t, J 6.5 Hz), 4.52 (1H, ddd, J 13.0, 10.0, 6.5 Hz). ^{13}C (125 MHz, CDCl_3) 3.35, 6.7, 15.1, 20.4, 53.8, 58.8, 63.8, 157.2, 197.9.

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