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Chiral enamide. Part 1: Epoxidations of chiral enamides. A viable approach to chiral nitrogen stabilized oxyallyl cations in [4+3] cycloadditions

Hui Xiong, Richard P. Hsung,*,† Lichun Shen and Juliet M. Hahn

Department of Chemistry, University of Minnesota, 207 Pleasant Street S.E., Minneapolis, MN 55455-0431, USA

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Abstract—The first study of stereoselective epoxidations of chiral enamides is described here. Its potential in the synthesis of chiral α-keto aminals as a viable approach to nitrogen stabilized oxyallyl cations in stereoselective [4+3] cycloadditions is also illustrated.

Allenamides and ynamides have attracted much attention in recent literature because they offer superior thermal stability and comparable reactivity relative to traditional ynamines and allenamines.[1–6] They present invaluable opportunities for developing new stereoselective methodologies.[3–6] Our investigations involving chiral allenamides[5] (**1**) and ynamides[6] (**2**) have frequently led us to products that contain the enamide functionality shown in **3** (Fig. 1). Comments suggesting that the fate of enamides is no more than a simple hydrolysis to ketones provoked us to examine this functional group carefully. The fate of enamides is clearly much more than the suggested less-fruitful hydrolysis.[7–9] However, in comparison with its celebrated structural relatives, enol ethers and enamines, reactivity of enamides is actually vastly under appreciated or non-systematically explored. This prompted us to launch a program examining reactivity of enamides. Specifically, we studied epoxidations[9] of chiral enamides **3** leading to α-keto aminals **6**. To the best of our knowledge, this is the first epoxidation study involving chiral enamides.[9] We envisioned that **6** can serve as an alternative approach to chiral nitrogen stabilized oxyallyl cations **7**,[5a,12,13] thereby providing a significant application of chiral enamides in stereoselective [4+3] cycloaddition chemistry.[10–14] We communicate here our preliminary findings along these efforts.

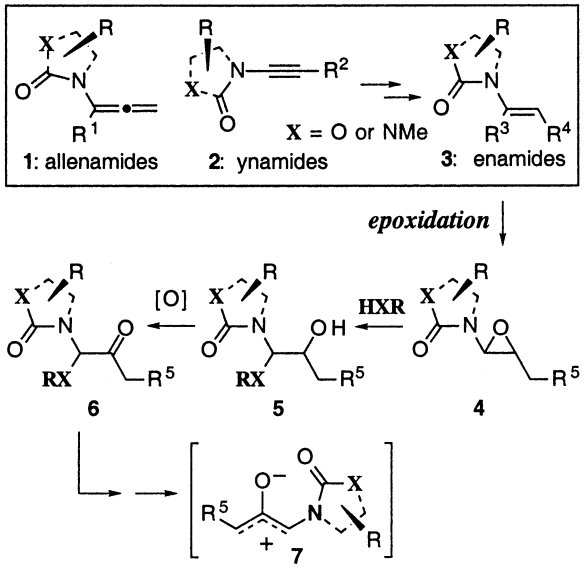

Figure 1.

Representative examples of acyclic or of cyclic enamides, prepared from condensation of aldehydes or ketones with oxazolidinones via standard dehydrative conditions,[15] were chosen to indicate scopes and generality of this study. As shown in Scheme 1, *m*-CPBA epoxidation of the enamide **8** in MeOH and in the presence of $NaHCO_3$ led to aminals **9** and **10**,[16] and subsequent acidic methanolysis of the mixture led exclusively to the aminal **10** in 44% overall yield. Subsequent oxidation led to the α-keto aminal **11** in 88% yield, thereby completing the proposed synthetic sequence for **6** shown in Fig. 1. Cyclic enamides **12** and **14**[17] could also be readily transformed using the same sequence to the α-keto aminals **13** and **15**, respectively

* Corresponding author. E-mail: hsung@chem.umn.edu
† A recipient of 2001 Camille Dreyfus Teacher–Scholar Award.

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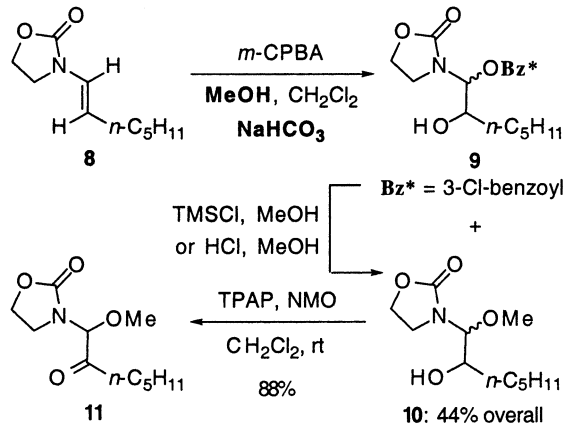
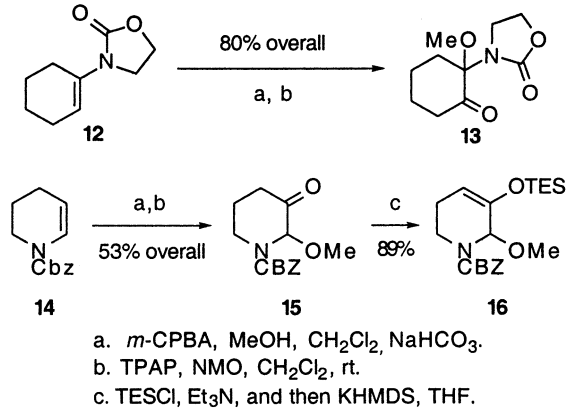


Scheme 1.

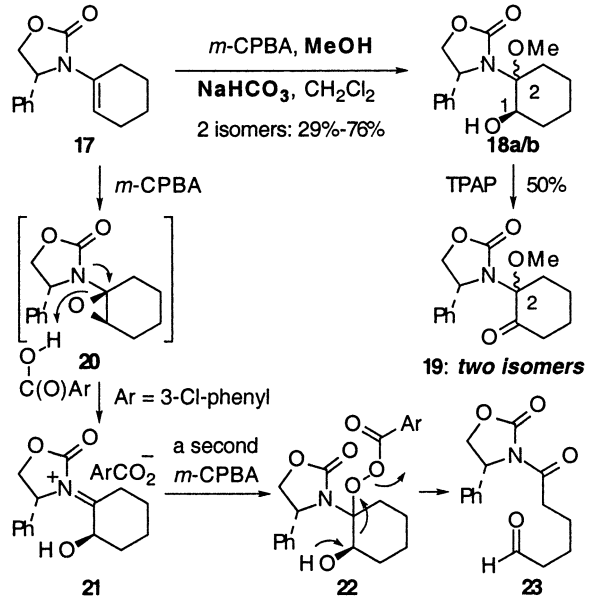
(Scheme 2). The α-keto aminal **15** was converted to the desired silyl enol ether **16** in 89% yield using KHMDS and TESCl.

Having established the feasibility in epoxidizing achiral enamides, epoxidiations of chiral enamides were examined for the level of diastereoselectivity. Epoxidation of **17** using *m*-CPBA in MeOH under buffered conditions led to the aminal **18** as two distinct diastereomers in a 1:1 ratio with a sporadic yield range (Scheme 3). Subsequent TPAP oxidation led to the α-keto aminal **19** but remained as two diastereomers. This led us to speculate that the diastereomeric ratio comes from the C2 aminal carbon and not C1.[18] An oxidative fragmentation was also observed when the epoxidation conditions involved MeOH and $NaHCO_3$, although only with chiral enamides, to give the keto aldehyde **23**[9a] presumably via **22**, thereby leading to sporadic yields for **18**.

This fragmentation could be avoided if the epoxidation was carried with MeOH or $NaHCO_3$ buffer leading to α-keto aminals **30a**/**b** and **31a**/**b** in excellent yields from enamides **24** and **25**, respectively (Scheme 4). Aminals **28a**/**b** and **29a**/**b** were obtained as a mixture of diastereomers [1.3:1], and oxidation of **28a**/**b** and **29a**/**b** either as a mixture or as individual diastereomers led to **30a**/**b** and **31a**/**b**, respectively, either as a mixture with equal ratio or one isomer. This confirms the earlier



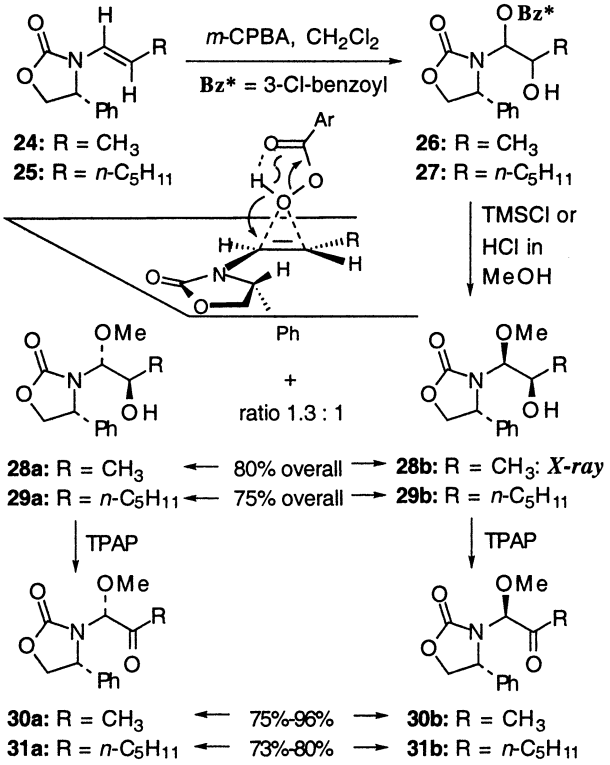
Scheme 2.



Scheme 3.

assertion that this epoxidation is highly stereoselective and that the diastereomeric ratio represents indiscriminant ring-opening of the epoxide at the aminal carbon. Based on the stereochemical assignment of **28a** via X-ray, epoxidation appears to favor the face away from the phenyl group (see insert) analogous to our findings in allenamide epoxidations.[5a]

Preparations of enol ethers from **30** and **31** appear not to be as forthright as with **15** in Scheme 2. The α-keto



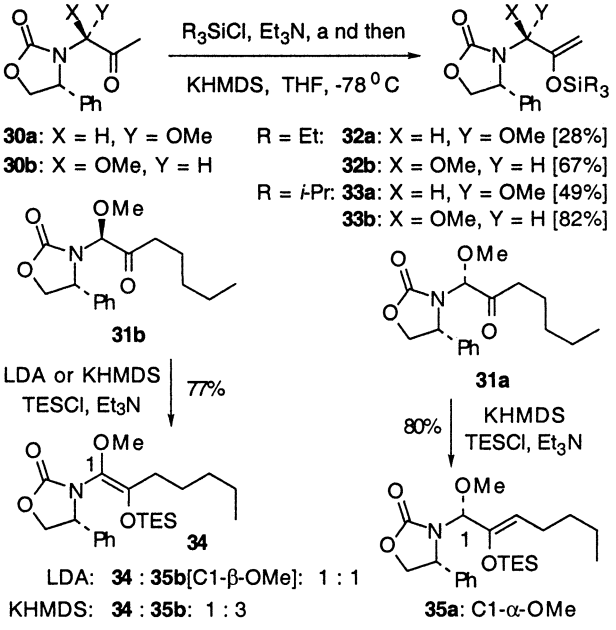
Scheme 4.

aminals **30a**/**b** provided either the TES (**32a**/**b**) or TIPS enol ethers or (**33a**/**b**) regioselectively if the ketone substrate was added to KHMDS in the presence of silyl chlorides (Scheme 5). On the other hand, while the α-keto aminal **31b** was not regioselective in this endeavor leading to a mixture of **34** and **35b** (the C1-OMe group is β) under several conditions, α-keto aminal **31a** (the C1-OMe group is α) was suitable to regioselectively provide the enol ether **35a**. We are not certain at this point why this contrast took place.

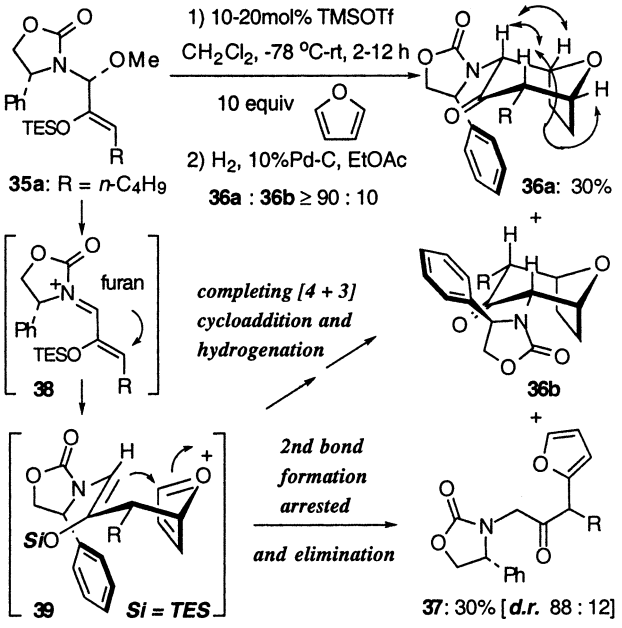
Syntheses of these silyl enol ethers allowed us to explore their potential in stereoselective oxyallyl cation [4+3] cycloadditions. However, thus far, the TES enol ether **35a** from the α-keto aminal **31a** was most successful in establishing the viability of this approach to stereoselective [4+3] cycloadditions. In the presence of 10–20 mol% of TMSOTf, **35a** reacted with furan to give the desired cycloadducts **36a**/**b** in 30% overall yield after hydrogenation with a ratio of ≥90:10 in favor of **36a** as assigned using NOE experiments (Scheme 6).

An equal amount of the hemi-cycloadduct **37** was isolated during many of these preliminary explorations, and conditions using other Lewis acids such as $SnCl_4$, $TiCl_4$ and BF_3–Et_2O did not improve the ratio of **36**:**37**. This preliminary result suggests that the desired *N*-acyl iminium salt **38** can be generated via a selective Lewis acid activation of the MeO group of **35a**, and that an ensuing 1,4-addition of the furan did occur to give the oxocarbenium intermediate **39**. However, the second bond formation did not compete well with the elimination leading to furan. This arrested second bond formation was not seen in analogous sulfur or oxygen stabilized oxyallyl cation.[11,14]

We are currently searching for other experimental protocols to resolve this particular challenge and will disclose details of this endeavor in due course. However, we are able to demonstrate here the first study of stereoselective epoxidation of chiral enamides, and its potential in generating chiral α-keto aminals as a viable source of chiral nitrogen stabilized oxyallyls in stereoselective [4+3] cycloadditions.



Scheme 5.



Scheme 6.

Acknowledgements

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18. Stereochemistry shown at C1 of **18a**/**b** was assigned later via NMR correlation with **28b**. The speculation of a stereoselective epoxidation of **17** was also supported by DMDO epoxidation of chiral enamide **25** (see Scheme 4) using DMDO-d_6 that generated from Oxone™ and acteone-d_6. This study led to the observation of a single 1-amido epoxide that was not stable but could be quickly characterized by ^{1}H NMR. ^{1}H NMR (500 MHz, acetone-d_6) δ 0.79 (t, 3H, $J=7.0$ Hz), 1.00–1.25 (m, 8H), 2.87 (t, 1H, $J=6.0$ Hz), 4.05 (dd, 1H, $J=6.0$, 9.0 Hz), 4.56 (s, 1H), 4.72 (t, 1H, $J=9.0$ Hz), 4.94 (dd, 1H, $J=6.0$, 9.0 Hz), 7.36–7.47 (m, 5H). This represents the first observation of a chiral 1-amido epoxide, although Adam had reported an account of achiral 1-amido epoxide (Ref. 9a).
19. Selected characterizations: **11**: $R_f=0.53$ (50% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3H, $J=6.8$ Hz), 1.27 (m, 4H), 1.56 (quintet, 2H, $J=7.2$ Hz), 2.54 (m, 2H), 3.42 (s, 3H), 3.51 (m, 2H), 4.39 (t, 2H, $J=8.3$ Hz), 5.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 22.3,

22.7, 31.1, 39.1, 39.5, 56.8, 62.6, 86.6, 158.7, 203.5; IR (thin film) cm^{-1} 2957s, 2928s, 2872s, 1755s, 1524w, 1483w, 1467m, 1415s, 1381m, 1239s, 1199s; mass spectra (CI) *m*/*e* (% relative abundance) 230 (70) M^++H, 198(42), 130(15), 128(33), 105(100), 88(38), 75(19); *m*/*e* Calcd for $C_{11}H_{20}NO_4$ 230.1392, found 230.1398. **18a**/**b**: R_f=0.29 (50% EtOAc in hexane); $[\alpha]_D^{20}$ −75.2 (*c* 0.5 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) major δ 1.20–2.20 (m, 8H), 3.15 (s, 3H), 4.01–4.04 (m, 1H), 4.17 (dd, 1H, *J*=2.5, 8.0 Hz), 4.60 (t, 1H, *J*=8.0 Hz), 4.95 (dd, 1H, *J*=2.5, 8.0 Hz), 7.27–7.41 (m, 5H); ^{13}C (300 MHz, $CDCl_3$) major δ 21.9, 22.0, 30.2, 30.9, 50.3, 58.2, 58.3, 70.5, 91.5, 126.2, 128.4, 129.0, 142.2, 158.1; IR (thin film) cm^{-1} 2943m, 1748s, 1334m, 1045w; mass spectrum (GC MS): *m*/*e* (% relative intensity) 259 (3) (M^+–MeOH), 162 (65), 104 (100), 91 (23). **23**: R_f=0.40 (50% EtOAc in hexane); $[\alpha]_D^{20}$ −72.8 (*c* 0.50 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.55–1.68 (m, 4H), 2.42–2.45 (m, 2H), 2.95–2.98 (m, 2H), 4.30 (dd, 1H, *J*=3.5, 8.5 Hz), 4.70 (t, 1H, *J*=8.5 Hz), 5.43 (dd, 1H, *J*=3.5, 8.5 Hz), 7.41–7.27 (m, 5H), 9.73 (t, 1H, *J*=1.5 Hz); ^{13}C (500 MHz, $CDCl_3$) δ 21.4, 23.5, 35.2, 43.5, 57.6, 70.0, 125.9, 128.7, 129.2, 139.1, 153.8, 172.2, 202.2; IR (thin film) cm^{-1} 3034m, 2944m, 1717s, 1435w, 1041m; mass spectrum (LC MS): *m*/*e* (% relative intensity) 276 (6) (M+H^+), 230 (45), 186 (67), 164 (66), 120 (100). **30a**: R_f=0.41 (50% EtOAc in hexane); $[\alpha]_D^{20}$ −52.2 (*c* 0.54 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 2.18 (s, 3H), 3.21 (s, 3H), 4.29 (dd, 1H, *J*=7.0, 9.0 Hz), 4.71 (t, 1H, *J*=9.0 Hz), 4.93 (dd, 1H, *J*=7.0, 9.0 Hz), 5.05 (s, 1H), 7.26–7.40 (m, 5H); ^{13}C (500 MHz, $CDCl_3$) δ 27.0, 57.0, 57.9, 70.7, 88.2, 127.4, 129.0, 129.1, 138.4, 153.8, 202.6; IR (thin film) cm^{-1} 2932m, 1756s, 1459m, 1002w; mass spectrum (GC MS): *m*/*e* (% relative intensity) 218 (2) (M^+–OMe), 206(100), 162(13), 135(23), 104(22), 103(35), 86(37), 77(12). **30b**: R_f=0.25 (50% EtOAc in hexane); $[\alpha]_D^{20}$ −153.9 (*c* 0.69 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.73 (s, 3H), 3.43 (s, 3H), 4.37 (dd, 1H, *J*=7.5, 9.0 Hz), 4.72 (t, 1H, *J*=9.0 Hz), 4.88 (dd, 1H, *J*=7.5, 9.0 Hz), 5.12 (s, 1H), 7.27–7.38 (m, 5H); ^{13}C (500 MHz, $CDCl_3$) δ 26.1, 56.8, 57.0, 70.3, 86.8, 128.5, 129.0, 129.7, 136.4, 158.6, 202.2; IR (thin film) cm^{-1} 2932m, 1756s, 1459m, 1002w; mass spectrum (GC MS): *m*/*e* (% relative intensity) 218 (2) (M^+–OMe), 206(100), 162(13), 135(28), 104(25), 103(35), 86(36), 77(12). **31a**: R_f=0.68 (50% EtOAc in hexane); $[\alpha]_D^{20}$ −61.1 (*c* 0.73 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J*=6.0 Hz), 1.21–1.32 (m, 4H), 1.51–1.56 (m, 2H), 2.47 (t, 2H, *J*=7.5 Hz), 3.19 (s, 3H), 4.29 (dd, 1H, *J*=5.5, 9.0 Hz), 4.70 (t, 1H, *J*=9.0 Hz), 4.92 (dd, 1H, *J*=5.5, 9.0 Hz), 5.09 (s, 1 H), 7.27–7.40 (m, 5H); ^{13}C (500 MHz, $CDCl_3$) δ 13.9, 22.4, 22.7, 31.2, 39.3, 57.0, 57.9, 70.7, 88.2, 127.4, 128.9, 129.0, 138.5, 158.6, 204.8; IR (thin film) cm^{-1} 2932m, 1758s, 1362m, 986w; mass spectrum (EI): *m*/*e* (% relative intensity) 274 (2) (M^+–OMe), 207(13), 206(100), 162(9), 135(15), 104(14), 86(15). **31b**: R_f=0.58 (50% EtOAc in hexane); $[\alpha]_D^{20}$ −123.5 (*c* 0.70 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, 3H, *J*=7.5 Hz), 0.98–1.04 (m, 3H), 1.06–1.18 (m, 3H), 2.03–2.16 (m, 2H), 3.42 (s, 3H), 4.34 (dd, 1H, *J*=7.5, 9.0 Hz), 4.71 (t, 1H, *J*=9.0 Hz), 4.87 (dd, 1H, *J*=7.5, 9.0 Hz), 5.15 (s, 1H), 7.27–7.37 (m, 5H); ^{13}C (500 MHz, $CDCl_3$) δ 13.9, 22.2, 22.3, 31.0, 39.0, 56.7, 56.8, 70.4, 86.5, 128.4, 128.98, 129.40, 136.7, 158.8, 204.3; IR (thin film) cm^{-1} 2954m, 1758s, 1374m, 1037w; mass spectrum (EI): *m*/*e* (% relative intensity) 274 (1) (M^+–OMe), 206(100), 162(8), 135(14), 86(14). **35a**: R_f=0.53 (50% ether in hexane); $[\alpha]_D^{20}$ 41.3 (*c* 0.45 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.70 (q, 6H, *J*=8.0 Hz), 0.92 (t, 3H, *J*=7.0 Hz), 0.99 (t, 9H, *J*=8.0 Hz), 1.30–1.33 (m, 4H), 1.95–2.00 (m, 1H), 2.11–2.18 (m, 1H), 3.19 (s, 3H), 4.19 (dd, 1H, *J*=6.0, 9.0 Hz), 4.58 (t, 1H, *J*=9.0 Hz), 4.78 (dd, 1H, *J*=6.0, 9.0 Hz), 4.85 (dt, 1H, *J*=1.0, 8.0 Hz), 5.21 (d, 1H, *J*=1.0 Hz), 7.26–7.33 (m, 5H); ^{13}C (500 MHz, $CDCl_3$) δ 5.3, 6.7, 13.9, 22.6, 24.6, 31.7, 55.6, 57.3, 70.7, 85.9, 112.2, 126.9, 128.3, 128.4, 140.6, 142.8, 159.2; IR (thin film) cm^{-1} 2969m, 2879m, 1774s, 1404m, 1239m, 1171m; mass spectrum (LC MS): *m*/*e* (% relative intensity) 420(78) (M+H^+), 388(100), 274(8). **36a**: R_f=0.48 (50% EtOAc in hexane); $[\alpha]_D^{20}$ −137.5 (*c* 0.40 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J*=7.0 Hz), 1.05–1.75 (m, 10H), 2.68 (ddd, 1H, *J*=6.0, 6.0, 6.0 Hz), 4.08 (dd, 1H, *J*=5.0, 9.0 Hz), 4.40 (dd, 1H, *J*=4.0, 7.0 Hz), 4.51 (ddd, 1H, *J*=2.0, 6.0, 6.0 Hz), 4.74 (t, 1H, *J*=9.0 Hz), 4,83 (d, 1H, *J*=4.0 Hz), 5.04 (dd, 1H, *J*=5.0, 9.0 Hz), 7.25–7.41 (m, 5H); ^{13}C (500 MHz, $CDCl_3$) δ 13.9, 22.7, 24.4, 25.7, 27.0, 29.5, 55.7, 58.3, 65.5, 71.2, 77.8, 79.9, 126.2, 128.8, 129.3, 140.5, 159.1, 204.4. IR (thin film) cm^{-1} 2957m, 2929m, 1761s, 1718s, 1457m, 1412m, 1399m, 1074m, 704m; mass spectrum (LC MS): *m*/*e* (% relative intensity) 344(38) (M+H^+), 326(64), 276(27), 232(29), 202(23), 176(78), 163(100), 132(30), 120(42). **37** (mixed with some pre-hydrogenated cycloadduct): R_f=0.55 (50% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$) pre-hydrogenated cycloadduct: δ 0.85 (t, 3H, *J*=7.0 Hz), 1.00–1.95 (m, 6H), 2.78 (dt, 1H, *J*=7.5, 6.0 Hz), 4.06 (dd, 1H, *J*=4.0, 9.0 Hz), 4.70 (m, 1H), 4.75 (dd, 1H, *J*=2.0, 6.0 Hz), 4.80 (t, 1H, *J*=9.0 Hz), 4.87 (dd, 1H, *J*=2.0, 4.5 Hz), 5.01 (d, 1H, *J*=4.5 Hz), 5.14 (dd, 1H, *J*=2.0, 6.0 Hz), 6.14 (dd, 1H, *J*=2.0, 6.0 Hz), 7.23–7.44 (m, 5H); **37**: δ 0.91 (t, 3H, *J*=7.5 Hz), 1.00–1.95 (m, 6H), 3.44 (d, 1H, *J*=18.0 Hz), 3.64 (dd, 1H, *J*=7.0, 8.0 Hz), 4.14 (t, 1H, *J*=8.0 Hz), 4.30 (d, 1H, *J*=18.0 Hz), 4.73 (t, 1H, *J*=8.0 Hz), 4.90 (t, 1H, *J*=8.0 Hz), 6.06 (d, 1H, *J*=3.5 Hz), 6.24 (dd, 1H, *J*=2.0, 3.5 Hz), 7.13–7.44 (m, 6H); ^{13}C (500 MHz, $CDCl_3$) δ as a mixture 13.77, 13.83, 22.3, 22.7, 24.7, 28.8, 29.2, 29.5, 49.2, 49.8, 55.6, 57.6, 59.7, 66.0, 70.1, 71.1, 80.4, 81.5, 107.7, 110.6, 126.1, 127.2, 129.0, 129.1, 129.2, 129.5, 132.9, 133.7, 136.7, 140.7, 142.2, 150.9, 158.5, 159.6, 202.2, 202.8; IR (thin film) cm^{-1} 2958m, 2928m, 1762s, 1723m, 1410m, 1399m, 1077m, 706m; mass spectrum (GC MS): *m*/*e* (% relative intensity) Peak 1: 341(30) (M^+), 281(5), 176(95), 150(60), 132(65), 91(78), 81(100); Peak 2: 341(5) (M^+), 281(7), 207(100), 176(10).