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Chemoselective deprotection of *N*-allylic amines using DDQ

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ABSTRACT

A highly chemoselective and simple method for the deprotection of *N*-allylic amines using DDQ has been developed. The use of DDQ in dichloromethane–water provides a mild and efficient one-step deallylation of a wide variety of orthogonally protected tertiary amine derivatives.

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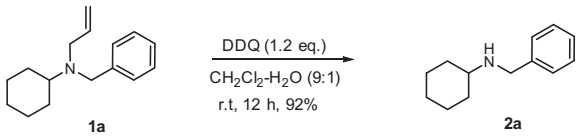
Protecting groups often play a crucial role in many complex synthetic strategies.[1] The choice of protecting groups is one of the decisive factors in the successful realization of a complex demanding synthetic project. The allyl moiety is a protecting group that permits orthogonal protection strategies with a wide range of protecting groups and thus finds increasing application in the synthesis of complex natural products.[2] The transition-metal-catalyzed methods[3] are the most widely and commonly used methods for allyl group deprotection. But selectivity can still be a problem, since *O*-allyl derivatives are cleaved faster than *N*-allyl derivatives in most cases. Reductive metals are not selective either.[4] An important drawback of the π-allyl–palladium methodology is the requirement of stoichiometric amounts of a nucleophilic compound, which acts as the allyl group scavenger. Selectivity is also a problem with chloroformate-mediated processes,[5] which are capable of cleaving different types of N–C bonds. New procedures involving Grubb's-type catalysts have also emerged in the last few years,[6] yet selectivity remains the problem with these methods. In view of this we became interested in the development of an alternative N-deallylation method that can smoothly provide free amines.

The high oxidation potential (E_0) of DDQ has resulted in the extensive use of this compound as a dehydrogenating agent in organic synthesis.[7] Even though *O*-allyl ethers are oxidatively cleaved in the presence of DDQ,[8] this reaction has not been developed further into a method of synthetic interest for the cleavage of *N*-allylic bond.[9] We now report that the *N*-allylic group can be cleaved oxidatively from a wide variety of orthogonally protected tertiary amine derivatives using DDQ as a dehydrogenating reagent.

Our studies began with the reaction of a series of allyl substrates on aliphatic, alicyclic, and benzylic amines. We carried out reaction initially by choosing compound **1a** as a model substrate (Scheme 1). DDQ was added to a solution of compound **1a** in dichloromethane–water (9:1) (Table 1, entry 1) and the resulting dark red solution stirred at room temperature overnight, during which time a pale yellow hydroquinone derivative was precipitated. The reaction proceeded smoothly, however it was found that correct work-up of the reaction was crucial. The optimized procedure involved extraction with several portions of CH_2Cl_2 and washing with saturated sodium bicarbonate solution, followed by loading the crude residue (after removal of the volatiles) directly onto a short basic alumina flash column, eluting with hexane–DCM to afford 92% yield of *N*-deallylated secondary amine **2a** (Table 1, entry 1).

The reaction was studied in a variety of solvents and the results are summarized in Table 1. It was observed that the presence of water and its amount along with an organic solvent plays an important role in the reaction. Decrease of the water ratio somewhat lowered the yield and increased the reaction time (Table 1, entry 2). In the absence of water, most of the amine **1a** was



Scheme 1.

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Table 1
Oxidative cleavage of compound **1a** with DDQ in various solvents at room temperature

Entry	Solvent system	DDQ (equiv)	Time (h)	Yield (%)
1	CH_2Cl_2–H_2O (9:1)	1.2	12	92
2	CH_2Cl_2–H_2O (9.7:0.3)	1.2	22	70
3	CH_2Cl_2	1.2	48	Trace
4	Hexane–H_2O (9:1)	1.2	24	0
5	Dioxane–H_2O (9:1)	1.2	10	Complex mixture
6	THF–H_2O (9:1)	1.2	12	Complex mixture
7	Toluene–H_2O (9:1)	1.2	36	45
8	$CHCl_3$–H_2O (9:1)	1.2	24	60
9	EtOAc–H_2O (9:1)	1.2	12	Complex mixture
10	MeOH–H_2O (9:1)	1.2	6	Complex mixture
11	CCl_4–H_2O (9:1)	1.2	24	20
12	MeCN–H_2O (9:1)	1.2	14	85

Table 2
Oxidative cleavage of compound **1a** with DDQ under various reaction conditions

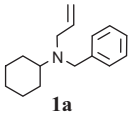
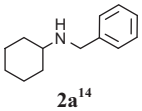
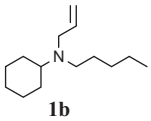
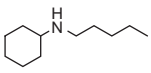
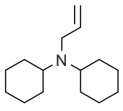
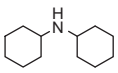
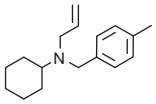
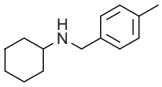
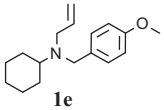
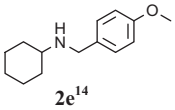
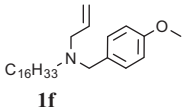
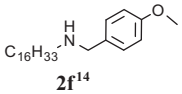
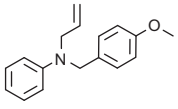
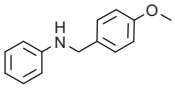
Entry	Reaction conditions	Time (h)	Yield (%)
1	0.8 equiv DDQ, CH_2Cl_2–H_2O (9:1) rt	20	45
2	1 equiv DDQ, CH_2Cl_2–H_2O (9:1) rt	18	80
3	1.2 equiv DDQ, CH_2Cl_2–H_2O (9:1) rt	12	92
4	1.2 equiv DDQ, CH_2Cl_2–H_2O (9:1) 0 °C	24	35
5	1.2 equiv DDQ, MeCN–H_2O (9:1) 70 °C	6	78

recovered (entry 3). No deallylation product was obtained when the reaction was carried out in hexane–water (entry 4). The reactions were performed in other solvents such as THF, toluene, $CHCl_3$, MeOH, CCl_4, MeCN, EtOAc, and dioxane (Table 1, entries 5–12). However, in most of the cases, a complex mixture was obtained (entries 5, 6, 9 and 10). The rate of the reaction became slower when $CHCl_3$, CCl_4, or toluene were used as the solvent (entries 7, 8, and 11). Interestingly, the yield of reaction in MeCN was comparable to that in CH_2Cl_2 (Table 1, entry 12). The use of 1.2 equiv of DDQ in a solvent mixture of CH_2Cl_2–H_2O (9:1) has an additional merit. The weakly acidic $DDQH_2$ (2,3-dichloro-5,6-dicyanohydroquinone) that precipitated during the reaction is almost insoluble in both CH_2Cl_2 and H_2O, so the reaction medium was constantly kept almost neutral as long as the reaction proceeded (Table 1, entry 1).[8–10]

This is sometimes very important in the case of substrates bearing acid-sensitive functional and protecting groups. Based on the above investigations; CH_2Cl_2 was preferred as the reaction media to perform the deallylation reaction.

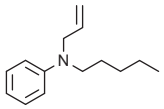
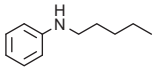
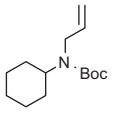
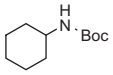
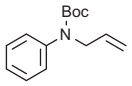
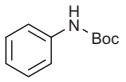
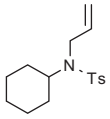
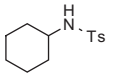
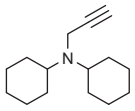
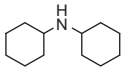
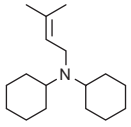
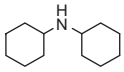
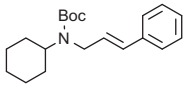
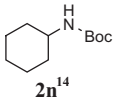
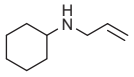
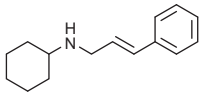
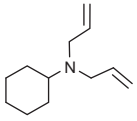
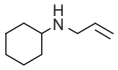
In principle, a stoichiometric amount of DDQ should be sufficient for the oxidative cleavage of *N*-allylic amines, however the reaction progressed slowly, probably because of competitive aqueous decomposition of DDQ.[11] To circumvent this problem, the DDQ was added in small portions every 20 min (3–4 portions) and this slow addition of DDQ resulted in high yield of products. Variation in the number of equivalents of DDQ was then examined (Table 2). Low yield of the product was obtained and mostly starting material

Table 3
Chemoselective deprotection of *N*-allylic amines[12]

S. No.	Substrate	Product	Time (h)	Yield[a] (%)
1	 **1a**	 **2a**[14]	12	92
2	 **1b**	 **2b**	18	85
3	 **1c**	 **2c**	18	90
4	 **1d**	 **2d**	12	80
5	 **1e**	 **2e**[14]	6	55
6	 **1f**	 **2f**[14]	7	50
7	 **1g**	 **2g**	3	35

(*continued on next page*)

Table 3 (*continued*)

S. No.	Substrate	Product	Time (h)	Yield[a] (%)
8	 **1h**	 **2h**	8	75
9	 **1i**	 **2i**	18	80
10	 **1j**	 **2j**	14	74
11	 **1k**	 **2k**	24	60
12	 **1l**	 **2l**	14	Complex mixture
13	 **1m**	 **2m**	4	95
14	 **1n**	 **2n**[14]	4	85
15	 **1o**	 **2o**	24	20
16	 **1p**	 **2p**	16	65
17	 **1q**	 **2o**  **2q**	48	10[b]

[a] Yields refer to chromatographically pure isolated compounds.
[b] Combined yield for the mixture of cyclohexanamine–*N*-allylcyclohexanamine in ratio 1:4.

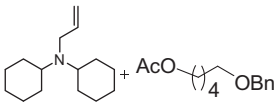
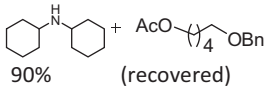
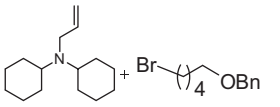
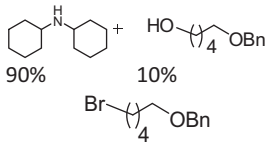
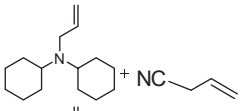
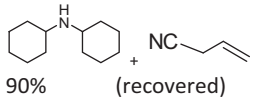
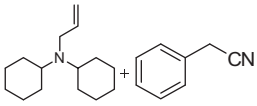
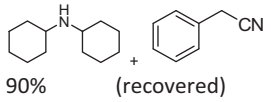
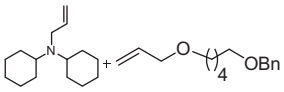
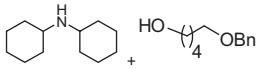
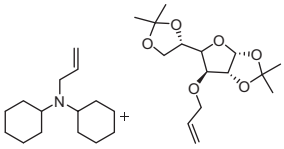
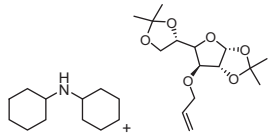
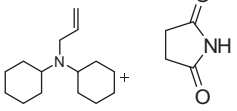
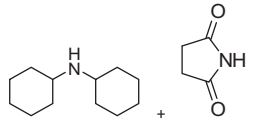
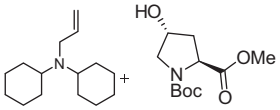
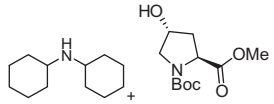
was recovered when less than 1 equiv of DDQ was used (Table 2, entry 1).

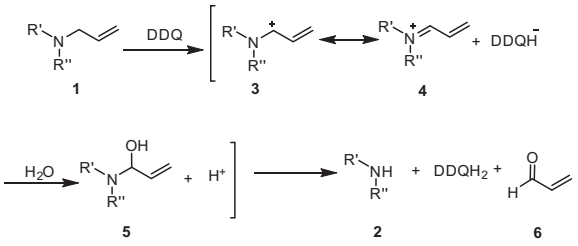
Use of 20% excess of DDQ brought about a large reduction in reaction time and significant increase in the yield (Table 2, entries 2 and 3). When the concentration of the reaction mixture was varied (between 0.4 and 0.02 M of starting material) it was found that the best combination of rate and ease of handling was at a concentration of approximately 0.1 M. Attempts to effect the reaction at temperatures lower than rt slowed the reaction considerably (Table 2, entry 4). An increase of temperature led to a faster conversion but the yield of deallylated amine was found to be lower (Table 2, entry 5).

Under the optimized reaction conditions, various substrates were subjected to the deallylation reaction[12] (Table 3). The reaction proceeded smoothly with aliphatic, alicyclic, or benzylic allyl amine substrates to give the corresponding secondary amines in good to excellent yields.

During this study, *N*-benzyl (*N*Bn), *N*-*t*-butyl carbamate (*N*Boc), and *N*-tosylamide (*N*Ts) groups were found to be stable to the reaction conditions (Table 3, entries 1, 4, 9, 10, 11, and 14). Selective

Table 4
Competitive one-pot reaction between *N*-allyl-*N*-cyclohexylcyclohexanamine and other reactants containing different functional groups

S. No.	Substrates	Products with yield	Time
1		 90% (recovered)	18
2		 90% 10% (recovered)	18
3		 90% (recovered)	18
4		 90% (recovered)	18
5		 90% 89%	18
6		 90% (recovered)	18
7		 90% (recovered)	18
8		 90% (recovered)	18



Scheme 2. A plausible mechanism for the cleavage of allylic amine.

deprotection of an *N*-allyl group in the presence of an *N*-PMB group could also be achieved under the conditions employed (Table 3, entries 5, 6 and 7). Deallylation of *N*-tosyl and *N*-Boc protected amine derivatives (Table 3, entries 9, 10, and 11) required longer reaction time and higher equivalents of oxidant DDQ (1.5–2.5 equiv). It has been observed that *N*-cinnamyl and *N*-prenyl systems (Table 3, entries 13 and 14) deprotected much faster than *N*-allyl substrates. But cleavage of *N*-propargyl amine (Table 3, entry 12) resulted in a complex reaction mixture. Extrapolation of the deprotection of tertiary allyl amines to secondary allyl amines was not very clear. Even though secondary amine *N*-cinnamylcyclohexanamine gave cyclohexanamine in 65% yield (Table 3, entry 16), conversion of *N*-allylcyclohexanamine to cyclohexanamine under the same reaction condition was very slow (Table 3, entry 15). When *N*,*N*-diallylcyclohexanamine was treated under the same condition (Table 3, entry 17), we obtained a mixture of compounds cyclohexanamine (**2o**) and *N*-allylcyclohexanamine (**2q**) even after 2 days, suggesting that secondary *N*-allylamines would require harsh reaction conditions to be cleaved.

In order to study the compatibility of this procedure with other functionalities, we carried out the one-pot competitive reaction between *N*-allylcyclohexylcyclohexanamine with other substrates containing different functional groups (Table 4).

N-Allyl group is selectively cleaved in the presence of benzyl and acetate groups (Table 4, entry 1). Similarly bromo- and cyano groups remain intact during the cleavage of the *N*-allyl group (Table 4, entries 2–4). When compounds with the *N*-allyl group and primary *O*-allyl groups were subjected to oxidative cleavage under the one-pot reaction conditions, both allyl groups were cleaved simultaneously (Table 4, entry 5). Interestingly we observed selectivity in the cleavage of the *N*-allyl group over the *sec*-*O*-allyl group in a one-pot reaction (Table 4, entry 6). Also the

imide, ester group, and Boc groups were found to be compatible under the reaction condition employed (Table 4, entries 7–8). Thus this method could synthetically be useful in the selective deprotection of the *N*-allyl group over the *sec*-*O*-allyl group and several other functionalities and thus may find application in the design and synthesis of complex natural products.

A plausible mechanism analogous to those reported for the cleavage of prenyl ethers, cinnamyl ethers, or OPMB[8a] is shown in Scheme 2. The reaction proceeds by the hydride abstraction from the activated methylene of allylic amine **1** by DDQ followed by trapping the iminium ion **4** by water giving a hemiaminal **5** which decomposes to give a secondary amine **2**, $DDQH_2$, and acrolein **6**. During the cleavage process the heteroatom nitrogen located at the α-position activates the adjacent allylic sp^3 C–H bond and further stabilizes the in situ formed intermediate. The oxidative cation formation appears to proceed through a sequence of radical cation formations followed by hydrogen atom abstraction. DDQ is a well-known electron acceptor and forms charge transfer (CT) complexes with a variety of donors indicated usually by an immediate color change in the reaction mixture.[13] In conclusion, we have demonstrated an alternative, convenient, and general method for the chemoselective cleavage of allylic amines[14] using DDQ-CH_2Cl_2–H_2O as a mild and efficient reagent.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.136.

References and notes

1. (a) Greene, T.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994; (c) Guibé, F. *Tetrahedron* **1997**, *53*, 13509.
2. Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 2056.
3. (a) Liu, Q.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511; (b) Carless, H. A. J.; Haywood, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 980; (c) Boss, R.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 558; (d) Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* **2004**, *45*, 5257.
4. Bertrand, M. P.; Escoubet, S.; Gastaldi, S.; Timokhin, V. I. *Chem. Commun.* **2002**, 216.
5. Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 3233.
6. (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781; (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2003**, *9*, 5793; (c) Alcaide, B.; Almendros, P.; Alonso, J. M.; Luna, A. *Synthesis* **2005**, 668.
7. Becker, H. In *The Chemistry of the Quinonoid Compounds*; Patai, S., Ed.; Wiley and Sons: Toronto, 1974; p 335.
8. (a) Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699; (b) Yadav, J. S.; Chandrasekhar, S.; Sumithra, G.; Kache, R. *Tetrahedron Lett.* **1996**, *37*, 6603; (c) Caputo, R.; Guaragna, A.; Palumbo, G.; Pedatella, S. *J. Org. Chem.* **1997**, *62*, 9369; (d) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. *Synlett* **1998**, 915; (e) Vatele, J.-M. *Synlett* **2002**, 507.
9. Bertrand, M.; Escoubet, S.; Gastaldi, S. *Eur. J. Org. Chem.* **2005**, 3855.
10. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
11. Buckle, D. R. In *Encyclopaedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 3, p 1699.
12. *General experimental procedure:* To a stirred solution of the *N*-allyllic amine (1 mmol) dissolved in 9 mL of CH_2Cl_2 and 1 mL of water, DDQ (1.2 equiv) was added intermittently in 3–4 portions.
Reaction progress was monitored by TLC. Upon consumption of the starting material, 2,3-dichloro-5,6-dicyanohydroquinone ($DDQH_2$) was removed by filtration. A saturated $NaHCO_3$ solution was added to the filtrate and the aqueous phase was extracted twice with CH_2Cl_2 (2 × 15 mL). Drying over Na_2SO_4, evaporation to dryness gave a material that was purified by flash column chromatography using neutral or basic alumina as stationary phase and hexane–CH_2Cl_2 (3:7) as eluent. The compound was characterized by comparison with authentic samples and by spectral data.
13. (a) Foster, R.; Foreman, M. L. In *The Chemistry of the Quinonoid Compounds, Part I*; Patai, S., Ed.; John Wiley & Sons: New York, 1974; p 257; (b) Buckley, D.; Dunstan, S.; Henbest, H. B. D. *J. Chem. Soc.* **1957**, 4880.
14. *Spectral data for selected compounds:*
*N-Benzylcyclohexanamine (**2a**):* Yellow liquid; IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 3071, 3065, 2980, 2933, 2854, 1580, 1455, 1372, 1264, 1212, 1119, 758. ^1H NMR (200 MHz, $CDCl_3$) δ 1.10–1.23 (m, 5H), 1.57–1.60 (m, 1H), 1.69–1.72 (m, 2H), 1.89–1.92 (d, *J* = 11.8 Hz, 2H), 2.17 (brs, 1H), 2.46–2.50 (m, 1H), 3.79 (s, 2H), 7.21–7.23 (m, 1H), 7.27–7.30 (m, 4H) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 26.0, 33.2, 50.7, 56.0, 126.8, 128.1, 128.3, 140.3 ppm.
*N-(4-Methoxybenzyl)cyclohexanamine (**2e**):* Yellow liquid; IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 3073, 3001, 2931, 2854, 1700, 1612, 1508, 1450, 1245, 1169, 1037, 819, 753. ^1H NMR (200 MHz, $CDCl_3$): δ 0.97–1.26 (m, 5H), 1.35–1.42 (m, 1H), 1.52–1.80 (m, 4H), 2.44–2.56 (m, 1H), 3.52 (s, 2H), 3.73 (s, 3H), 4.16 (brs, 1H), 6.75–6.80 (d, *J* = 8.6 Hz, 2H), 7.20–7.23 (m, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.2, 25.5, 29.6, 49.9, 55.6, 57.5, 112.9, 126.5, 130.2, 157.8 ppm
*N-(4-Methoxybenzyl)hexadecan-1-amine (**2f**):* Pale yellow viscous oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3478, 3071, 2975, 2852, 1728, 1612, 1511, 1645, 1248, 1171, 1039, 817, 760. ^1H NMR (200 MHz, $CDCl_3$): δ 0.87–0.93 (t, 3H), 1.37–1.35 (m, 29H) 2.49–2.57 (m, 2H), 3.61 (s, 2H), 3.82 (s, 3H), 6.84–6.88 (m, 2H), 7.23–7.28 (m, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.3, 20.9, 25.1, 25.6, 27.6, 27.8, 27.9, 30.2, 51.5, 53.4, 55.5, 111.7, 128.2, 129.9, 156.7 ppm. Anal. Calcd for $C_{24}H_{43}NO$: C, 79.72; H, 11.99; N, 3.87%; Found: C, 79.74; H, 11.95; N, 3.92%.
*tert-Butylcyclohexylcarbamate (**2n**):* White solid; mp 74–76 °C; IR ($CHCl_3$, cm^{-1}): ν_{max} 3356, 2984, 2934, 2822, 2713, 1720, 1658, 1452, 1416, 1263, 830. ^1H NMR (200 MHz, $CDCl_3$): δ 1.05–1.36 (m, 5H), 1.44 (s, 9H), 1.58–1.71 (m, 3H), 1.90–1.95 (m, 2H), 3.39–3.42 (m, 1H), 4.43 (brs, 1H) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ 24.8, 25.4, 28.3, 33.4, 49.3, 78.8, 155.1 ppm.