Pergamon

Tetrahedron 57 (2001) 5879–5883

TETRAHEDRON

Investigation of 1-bromo-3-buten-2-one as building block in organic synthesis

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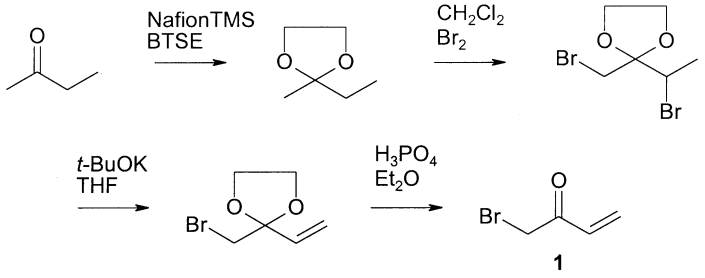
Received 7 February 2001; revised 20 April 2001; accepted 10 May 2001

Abstract—1-Bromo-3-buten-2-one is investigated as a building block for organic synthesis. Reduction to the corresponding alcohol works best with lithium aluminium hydride, reaction with primary amines gives 5-membered-aza-heterocycles in moderate yields and reaction with activated methylene compounds to form 5-membered-carbocycles gave unsatisfactory yields when a one-pot-procedure was used. The first step of a stepwise protocol, a Michael addition, is discussed.

1. Introduction

A procedure for the synthesis of 1-bromo-3-buten-2-one **1** has previously been reported (Scheme 1).[1] Compound **1** has three electrophilic sites in a C4 skeleton (Fig. 1). Reactions of **1** with nucleophilic species can, therefore, take place at three locations, making this compound a potentially valuable and versatile building block for organic synthesis. Compared to the corresponding classical 1,4-dibromo-2-butanol,[2] our synthon offers at least two advantages. First, it is cleaner since one electrophilic end has no leaving group. Consequently, the addition does not generate any byproduct with one less bromine atom to eliminate. Secondly, the electrophilic sites are of differing nature, and it should be possible to obtain regiocontrol of nucleophilic attack when required. In this paper we present



Scheme 1.

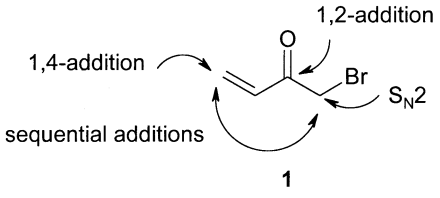


Figure 1.

reactions of bromenone **1** with three different types of nucleophiles: complex hydrides, primary N-nucleophiles and C-nucleophiles derived from activated methylene compounds. These reactions provide insight into the electrophilicity of the three sites relative to each other. We have also investigated the possibility of one-pot sequential addition, first via an inter- then an intramolecular process, with the latter competing with a second intermolecular process.

Ketone **1** is stable in solution for some days in the refrigerator, but starts to polymerise upon concentration. Therefore, freshly prepared **1** was used in all reactions described later.

Keywords: annulation; keto acids and derivatives; Michael reactions; pyrrolidines/pyrrolidinones.

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0040–4020/01/$ - see front matter
PII: S0040-4020(01)00526-9

2. Results and discussion

2.1. Attempts to synthesize 1-amino ketones

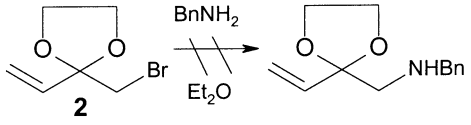
Protection of the carbonyl as a ketal leaves bromine as the sole reactive site towards nucleophiles by deactivating the double bond. Attempts to prepare 1-aminosubstituted ketone, from the acetal precursor **2**, were unsuccessful. For instance, benzyl amine and **2** were mixed under different reaction conditions:

solvents: pentane, 1,4-dioxane, methanol, $CHCl_3$/*t*-BuOH (3/1);
base: K_2CO_3, *t*-BuOK;
temperature: room temperature, reflux;
reaction time: 1 h to 3 d.

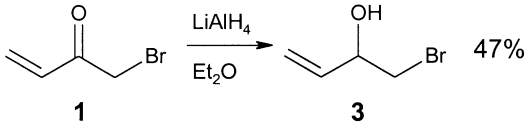
No reaction was observed regardless of the experimental conditions (Scheme 2). This was attributed to steric hindrance by the dimethylene acetal unit. There may also be an electronic effect from the lone pairs on oxygen that may repel the attacking nucleophile and hence, lower the reactivity.

2.2. Hydride reduction

Ketone **1** was reduced to alcohol **3** with lithium aluminium hydride. Sodium borohydride gave a less reproducible reduction with a lower yield. In neither case was the formation of the epoxide observed (Scheme 3).[3] Formation of epoxide is otherwise often a common feature in bromohydrin synthesis.



Scheme 2.



Scheme 3.

2.3. Amine-nucleophiles

Sequential addition of a primary amine to both ends of bromenone **1** would afford a highly interesting pyrrolidinone or pyrrolidinol ring. This type of heterocycle is found in many bioactive products such as antibiotics (pallidiflorine, actinomycin X1a), toxins and bioactive peptides.[4]

When bromenone **1** was reacted with a primary amine in the presence of potassium carbonate in diethyl ether the first step that seemed to take place (as monitored by NMR spectroscopy) was the nucleophilic displacement of bromine. A new vinylic system was observed [R=Bn: δ 5.87 (dd, 1H, J=10.3, 17.1 Hz), 5.53 (dd, 1H, J=1.7, 17.1 Hz), 5.29 (dd, 1H, J=1.7, 10.3 Hz)]. A similar strategy to form a heterocyclic ring has been used to prepare a thiophene ring with the bromoketone moiety reacting first.[5] Change from bromine to chlorine reversed the reaction order in that case.

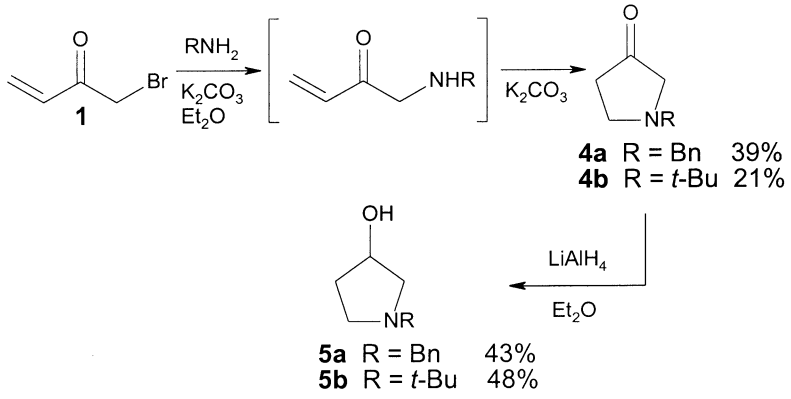
This does not prove that all of **1** reacts by this pathway, but it is clear that at least a considerable amount does so. The ring closure expected to follow was, therefore, of the disfavoured 5-*endo*-trig type according to Baldwin's rules. This is probably why the pyrrolidinones and then pyrrolidinols form only in moderate yields, with polymerisation of the intermediates as competing reactions (Scheme 4).

Reaction in the presence of other bases such as sodium bicarbonate, triethylamine, sodium hydride and pyridine were tried without any improvement. Dichloromethane was also used as solvent but the reaction gave even more side products and polymerisation.

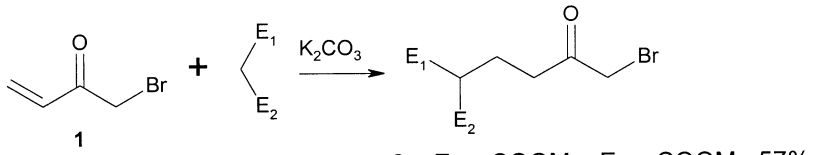
This approach to form a 5-membered heterocycle by an S_N2-intramolecular Michael sequence may work better with larger substrates. With larger substrates, the initially formed Michael product should be less prone to polymerisation due to steric hindrance.

With aniline, traces of the desired product were observed by NMR but never isolated. Most of the aniline was recovered during the final distillation (90–95%).

All of the *N*-substituted 3-pyrrolidinones were very sensitive towards air. This was established by a colour change



Scheme 4.



6a E_1 = COOMe E_2 = COOMe 57%
6b E_1 = COOEt E_2 = COOEt 53%
6c E_1 = COOEt E_2 = COMe 62%
6d E_1 = COMe E_2 = COMe 64%

Scheme 5.

Table 1. Synthesis of Michael adduct **6**

E_1, E_2	Solvent	Base (equiv.)	Temperature	Time (h)	Yield (%)
CO_2Et	Diethyl ether	2 K_2CO_3	rt	24	54
		1 K_2CO_3	rt	24	53
		0.2 K_2CO_3/Al_2O_3[a]	rt	24	19[b]
		1 K_2CO_3, 1 TMSCl	Reflux	48	53
		1 K_2CO_3, 5 $NaHCO_3$	Reflux	96	80
	Acetonitrile	1 K_2CO_3	rt	24	32
		0.25 K_2CO_3	Reflux	16	41[b]
		0.25 K_2CO_3, 8 $NaHCO_3$	Reflux	16	49[b]
	THF	1 K_2CO_3	rt	24	53
CO_2Me	THF	1 K_2CO_3	rt	24	57
CH_3CO CO_2Et	Diethyl ether	1 K_2CO_3	rt	24	64
CH_3CO		1 K_2CO_3	rt	24	62

[a] K_2CO_3/Al_2O_3 was prepared accoridng to Ref. [7].
[b] Cyclisation product was observed.

from colourless to yellow, to green, then to black within a few minutes. An increased yield of *N*-substituted pyrrolidine derivatives was obtained when the pyrrolidinones were directly reduced to pyrrolidinols prior to isolation. Yields are given in Section 4.

2.4. Carbon-nucleophiles

The Michael addition makes it easy to obtain multifunctional molecules. We attempted to utilise this process by the addition of carbon-nucleophiles derived from activated methylenes to ketone **1**. These carbanion reagents inverted the priority order between bromine and enone observed during the addition of amines. Unfortunately, we were unable to establish an efficient protocol for further cyclising products **6** to carbocycles (Scheme 5). In these attempts to run a one-pot synthesis, complex reaction mixture were obtained. No attempts were made to isolate these products. In one case, the one-pot procedure gave a modest 13% isolated yield of 3-oxo-cyclopentane-1,1-dicarboxylic acid diethyl ester (*t*-BuOK, 1 h in dry diethyl ether) with an NMR spectrum in accordance with the literature.[6] When the reaction was performed under ultrasonic activation in a bath, GC showed the formation of the desired product only (12 h, 15% conversion, reaction rate declining). We considered the reaction rate to be too low for practical applications. Thus, a stepwise reaction sequence including isolation of intermediate **6** has been considered. The most interesting results can be seen in Table 1.

The formation of the cyclopentanone is very slow. We believe that the methylene anion, formed after the Michael addition, is responsible for problems with polymerisation and formation of side products. It is clearly more reactive than the methine anion, and causes both dimerisation and Favorskii rearrangements.

Surprisingly, the addition of trimethylsilyl chloride to trap the intermediate enolate did not help, but addition of sodium bicarbonate increased the yield considerably. We believe that the hydrogen carbonate ion protonates the enolate. The yield increased for all substrates (usually by 10–15%) with the best result obtained in the case of diethyl ester. Unfortunately, the reaction time also increased considerably (from 24 to 96 h).

3. Conclusion

We have investigated the reactivity of bromobutenone **1** as a building block to form functionalised pyrrolidines and cyclopentanones. All three electrophilic sites present can be selectively involved. This study showed that the order of reactivity between bromine and enone is reversed depending on the reagent, amines or C-nucleophiles. Heterocycles can be obtained through a sequential double addition with yields bound to the stability of the products.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were obtained on a Jeol Eclipse 400 (399.65 MHz) spectrometer with $CDCl_3$ as solvent. All

coupling constants are measured in Hz. GC analyses were performed on a Varian 3300 gas chromatograph equipped with a CP-sil-8 (25 m, 0.32 mm i.d.) column. Analyses by gas chromatography mass spectrometry were carried out on a Hewlett Packard 5890 Series II gas chromatograph equipped with a Supelco SPB 5 (25 m, 0.25 mm i.d.) column connected to a VG Analytical Tribid mass spectrometer. Mass spectra were recorded using EI ionisation (70 eV) and the ion source temperature was 180°C. Infrared spectra were recorded on a Shimadzu IR-470 and a Perkin Elmer FTIR-1600 infrared spectrometer. *Purum* and *puriss* quality chemicals were used as delivered. Compounds **1** and **2** were synthesised according to literature.[1] Diethyl ether was distilled from sodium and benzophenone.

4.1.1. 1-Bromo-3-buten-2-ol 3. Compound **1** (3 mmol, 347 mg) was dissolved in dry diethyl ether (20 ml) and cooled on an ice bath. The entire system was purged with argon and lithium aluminium hydride (1.5 mmol, 57 mg) was added. The reaction was stirred for 2 h before seven drops of water (~9 mmol) were added. The reaction was left stirring for another 2 h before it was filtered on a sintered funnel. The solid was washed twice with diethyl ether (10 ml) and the filtrate was dried over magnesium sulphate, filtered and the solvent was removed. The product was obtained by Kugelrohr distillation. Yield 213 mg (47%.), colourless oil; bp 70–74°C, 16 mmHg (lit. 70–74°C, 10 mmHg, 54–55°C, 6 mmHg).[8] ^{1}H NMR δ 5.85 (ddd, 1H, J=5.3, 10.4, 17.3 Hz), 5.37 (ddd, 1H, J=1.3, 1.3, 17.3 Hz), 5.25 (ddd, 1H, J=1.3, 1.3, 10.4 Hz), 4.32–4.37 (m, 1H), 3.52 (dd, 1H, J=3.9, 10.3 Hz), 3.38 (dd, 1H, J=7.2, 10.3 Hz), 2.28 (d, 1H, J=4.8 Hz). ^{13}C NMR δ 137.8, 117.5, 71.9, 39.0. IR (neat) 3420 (br), 3010. NMR spectra are in accordance with literature.[9]

4.2. General procedure for synthesis of *N*-substituted 3-pyrrolidinones

Compound **1** (1 mmol, 149 mg) was dissolved in diethyl ether (40 ml) and cooled to −40°C whereafter potassium carbonate (2 mmol, 276 mg) was added. A dropping funnel was charged with the amine (benzyl or *t*-butyl, 1 mmol) dissolved in diethyl ether (40 ml). The entire system was purged with argon and the amine solution was added dropwise over a period of 1 h. The reaction mixture was allowed to reach room temperature and was then left with stirring overnight (24 h). The reaction mixture was heated to reflux for 1 and 8 h for benzyl and *t*-butyl, respectively. The reaction mixture was filtered through a sintered funnel and the remaining salt was washed twice with diethyl ether (5 ml) and the filtrate was dried over magnesium sulphate. The drying agent was filtered off and the solvent was removed. The product was obtained by Kugelrohr distillation.

4.2.1. *N*-Benzyl 3-pyrrolidinone 4a. Yield 68 mg (39%), colourless oil; bp 76–78°C, 0.01 mmHg (FLUKA, 76–77°C, 0.01 mmHg). ^{1}H NMR δ 7.34 (m, 5H), 3.73 (s, 2H), 2.96 (s, 2H), 2.94 (t, 2H, J=6.9 Hz), 2.42 (t, 2H, J=6.9 Hz). ^{13}C NMR δ 214.2, 137.5, 128.7, 128.4, 127.4, 61.5, 60.7, 51.3, 38.0. ^{1}H NMR spectra was in accordance with the commercial product (FLUKA).

4.2.2. *N-t*-Butyl 3-pyrrolidinone 4b. Yield 30 mg (21%), colourless oil (sometimes pale yellow); bp 81–85°C, 14 mmHg. ^{1}H NMR δ 3.06 (s, 2H), 2.99 (t, 2H, J=6.8 Hz), 2.42 (t, 2H, J=6.8 Hz) 1.11 (s, 9H). ^{13}C NMR δ 215.3, 55.1, 52.5, 43.6, 38.2, 25.3. IR (neat) 1765, 1255, 1230. HRMS 141.1160 (M^+). $C_8H_{17}NO$ requires 141.1153. GC/MS *m/z* (relative intensity) 141 (9), 127 (9), 126 (85), 85 (13), 84 (13), 71 (31), 70 (100), 69 (18), 68 (16), 67 (19), 58 (57), 57 (88), 56 (65), 55 (58), 54 (27).

4.3. General procedure for synthesis of *N*-substituted 3-pyrrolidinols

Compound **1** (1 mmol, 149 mg) was dissolved in dry diethyl ether (40 ml) and cooled to −40°C and then potassium carbonate (2 mmol, 276 mg) was added. A dropping funnel was charged with amine (benzyl or *t*-butyl, 1 mmol) dissolved in dry diethyl ether (40 ml). The system was purged with argon and the amine solution was added dropwise over a period of 1 h. The reaction was allowed to reach room temperature and was then left, with stirring, overnight (24 h). The reaction mixture was heated to reflux 1 and 6 h for benzyl and *t*-butyl, respectively. Lithium aluminium hydride (1 mmol, 38 mg) was added and the mixture was stirred for 2 h and then five drops of water were added (~6 mmol). The reaction mixture was stirred for another 2 h and then filtered on a sintered funnel and the remaining salt was washed twice with diethyl ether (5 ml) and the filtrate was dried over magnesium sulphate. The drying agent was filtered off and the solvent was removed. The product was obtained by Kugelrohr distillation.

4.3.1. *N*-Benzyl 3-pyrrolidinol 5a. Yield 76 mg (43%), colourless oil; bp 113–115°C, 2 mmHg (FLUKA, 113–115°C, 2 mmHg). ^{1}H NMR δ 7.29 (m, 5H), 4.30 (m, 1H), 3.60 (s, 2H), 2.83 (ddd, 1H, J=4.2, 8.3, 8.3 Hz), 2.65 (dd, 1H, J=2.2, 10.0 Hz) 2.50 (dd, 1H, J=5.1, 10.0 Hz) 2.30–2.50 (br, 1H), 2.08–2.34 (m, 2H), 1.63–1.77 (m, 1H). ^{13}C NMR δ 138.7, 128.8, 128.2, 127.0, 71.3, 62.9, 60.1, 52.3, 34.9. ^{1}H NMR spectrum was in accordance with literature.[10]

4.3.2. *N-t*-Butyl 3-pyrrolidinol 5b. Yield 69 mg (48%), colourless oil; bp 99–102°C, 14 mmHg. ^{1}H NMR δ 4.28 (m, 1H), 2.65–3.00 (br, 1H), 2.82 (ddd, 1H, J=6.0, 8.6, 8.7 Hz), 2.72 (dd, 1H, J=5.1, 10.1 Hz), 2.62 (dd, 1H, J=2.5, 10.1 Hz), 2.50 (ddd, 1H, J=6.0, 8.7, 8.9 Hz), 1.98–2.16 (m, 1H), 1.62–1.77 (m, 1H), 1.04 (s, 9H). ^{13}C NMR δ 71.0, 55.2, 52.1, 44.2, 34.6, 25.9. IR (neat) 3380 (br), 1240, 1230. HRMS 143.1304 (M^+). $C_8H_{17}NO$ requires 143.1310. GC/MS *m/z* (relative intensity) 143 (7), 129 (13), 128 (100), 110 (9), 70 (17), 57 (14).

4.4. General procedure for the Michael addition reactions

The activated methylene compound (see Table 1, 1 mmol) was dissolved in 10 ml of dry diethyl ether and potassium carbonate (1 mmol, 138 mg) was added. Here sodium bicarbonate (5 mmol, 420 mg) can be added to increase the yield. Compound **1** (1 mmol, 149 mg) dissolved in 10 ml of dry diethyl ether was added in one portion. The reaction was left stirring at room temperature for 24 h (96 h with sodium bicarbonate). The reaction mixture was filtered through a short plug of silica and the plug was washed with

20 ml of diethyl ether. The solvent was removed and the product was obtained by flash chromatography (petroleum ether/diethyl ether 70:30).

4.4.1. 2-(4-Bromo-3-oxo-butyl)-malonic acid dimethyl ester 6a. Yield 162 mg (57%), colourless oil. Purity 98%. ^{1}H NMR δ 3.85 (s, 2H), 3.71 (s, 6H), 3.42 (t, 1H, J=7.2 Hz), 2.75 (t, 2H, J=7.2 Hz), 2.17 (dt, 2H, J=7.2, 7.2 Hz). ^{13}C NMR δ 200.8, 169.4, 52.7, 50.1, 36.7, 34.0, 22.7. IR (neat) 1750, 1720. HRMS, no molecule ion was observed. High-resolution mass determination was made using the [M^+−MeO]-ion. Observed 250.9718 and 248.9772. $C_8H_{10}BrO_4$ requires 250.9742 and 248.9762. GC/MS *m/z* (relative intensity) 249, 251 (6, M−MeO), 217, 219 (16), 187 (48), 155 (100), 121, 123 (8), 113 (76), 93, 95 (8), 69 (22), 59 (39), 55 (47).

4.4.2. 2-(4-Bromo-3-oxo-butyl)-malonic acid diethyl ester 6b. Yield 177 mg (53%), colourless oil. Purity 98%. ^{1}H NMR δ 4.18 (q, 4H, J=7.1 Hz), 3.86 (s, 2H), 3.38 (t, 1H, J=7.2 Hz), 2.77 (t, 2H, J=7.2 Hz), 2.18 (dt, 2H, J=7.2, 7.2 Hz), 1.25 (t, 6H, J=7.1 Hz). ^{13}C NMR δ 200.8, 168.9, 61.5, 50.3, 36.7, 33.9, 22.5, 14.0. IR (neat) 1750, 1720. HRMS, no molecule ion was observed. High-resolution mass determination was made using the [M^+−EtO]-ion. Observed 264.9894 and 262.9906. $C_9H_{12}BrO_4$ requires 264.9898 and 262.9919. GC/MS *m/z* (relative intensity) 263, 265 (6, M−EtO), 215 (26), 169 (82), 141 (34), 127 (58), 93, 95 (14), 55 (100).

4.4.3. 2-Acetyl-6-bromo-5-oxo-hexanoic acid ethyl ester 6c. Yield 173 mg (62%), colourless oil. Purity >98%. ^{1}H NMR δ 4.19 (dq, 2H, J=1.2, 7.1 Hz), 3.86 (s, 2H), 3.50 (t, 1H, J=7.1 Hz), 2.73 (t, 2H, J=7.0 Hz), 2.24 (s, 3H), 2.13 (dq, 2H, J=2.8, 7.1, 7.1 Hz), 1.27 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 202.7, 201.2, 169.4, 61.7, 57.9, 36.8, 34.0, 29.2, 21.8, 14.2. IR (neat) 1735, 1710. HRMS, no molecule ion was observed. High-resolution mass determination was made using the [M^+−EtO]-ion. Observed 234.9796 and 232.9804 (M^+−EtO). $C_8H_{10}BrO_3$ requires 234.9793 and 232.9813. GC/MS *m/z* (relative intensity) 236, 238 (4, MCH_3CO), 233, 235 (4, M−EtO), 185 (35), 157 (34), 139 (28), 121, 123 (4), 111 (23), 93, 95 (3), 55 (44), 43 (100).

4.4.4. 5-Acetyl-1-bromo-heptane-2,6-dione 6d. Yield 159 mg (64%), colourless plates. Purity 97%. Mp 41.5–46.0°C. ^{1}H NMR δ 3.85 (s, 2H), 3.68 (t, 1H, J=7.0 Hz), 2.67 (t, 2H, J=7.0 Hz), 2.20 (s, 6H), 2.12 (q, 2H, J=7.0 Hz) and for the enol form 16.74 (s, 1H), 3.87 (s, 2H), 2.76 (t, 2H, J=7.8 Hz), 2.57 (t, 2H, J=7.8 Hz), 2.15 (s, 6H). Roughly 60/40. ^{13}C NMR δ 203.9, 201.3, 201.2, 191.3, 108.6, 67.6, 40.1, 36.9, 34.1, 34.0, 29.4, 23.1, 22.0, 21.6. IR (neat) 3445 (br) 3010, 1720, 1700. No HRMS due to decomposition during transport. GC/MS *m/z* (relative intensity) 248, 250 (1, M^+), 206, 208 (3), 155 (4), 127 (69), 121, 123 (6), 113 (48), 109 (39), 93, 95 (10), 85 (20), 71 (31), 55 (26), 43 (100).

Acknowledgements

We thank Professor E. Uggerud for high-resolution mass spectral analyses. We also thank the Research Council of Norway for generous financial support.

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