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Studies related to the total synthesis of the sesquiterpene core of the pyrrolobenzoxazine natural products CJ-12662 and CJ-12663

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ABSTRACT

A highly effective procedure is reported to synthesize a substituted bicyclo[4.2.0]octenol derivative by regioselective cycloaddition of phenyl-1-propynyl sulfide with cyclohexenone followed by selective reduction of the ketone group and reductive elimination of phenylsulfonyl group. The strained cyclobutene ring was then engaged in a ring-opening/cross metathesis sequence in the presence of Hoveyda–Grubbs 2nd generation catalyst. The synthesis serves as a model study toward the synthesis of the sesquiterpene diol portion of the terpenoid pyrrolobenzoxazine alkaloids, CJ-12662 and CJ-12663.

Natural product alkaloids of the general formula **A** (Fig. 1) have been isolated from the fermentation broth of *Aspergillus fischeri* var. *thermomutatus* ATCC 18618.[1] They belong to a unique class of terpenoid pyrrolobenzoxazine alkaloids which display broad antiparasitic and antibiotic properties. A single-crystal structure determination established that CJ-12662 and CJ-12663 contain a pyrrolobenzoxazine carboxylic acid esterified with a sesquiterpene diol (Fig. 1).[2]

The alkaloid cores of CJ-12662 and CJ-12663 have been synthesized by the groups of Barrett and Baldwin, respectively.[2,3] There are currently no reports on the total synthesis of the sesquiterpene core of these natural products. This challenging terpenoid structure is a *cis*-decalin containing no less than six stereocenters and three contiguous oxygenated functional groups. The general strategy we have envisioned for the total synthesis of this terpene is depicted in Scheme 1. We had planned to construct ring A and the *cis*-diol by a stereodirected pinacol coupling (disconnection a).

The most challenging part of the synthesis is the stereoselective construction of the two vicinal olefinic side chains with simultaneous control of the configuration of the double bond of the allylic acetate. The cis-relationship between the two vicinal carbon chains

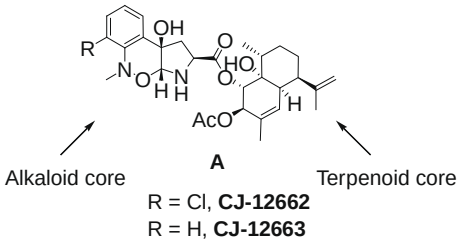

Figure 1. Structure of terpenoid pyrrolobenzoxazine alkaloids CJ-12662 and CJ-12663.

could be established by a regio- and stereoselective cycloaddition reaction (step d) of an activated acetylene to the less hindered face of (*R*)- 6-methylcyclohexenone. A ring opening metathesis of the cyclobutene ring coupled with a cross metathesis (step c) with an allylic acetate derived (step e) from (*R*)-glyceraldehyde would generate an advanced intermediate for the pinacol coupling. This Letter reports some model studies on the cycloaddition and ROM/CM reactions performed on cyclohexenone.

[2+2] Cycloadditions of acetylenes to electron-deficient olefins have been studied by several groups.[4] Best yields have been obtained in the presence of a Lewis acid catalyst. We selected

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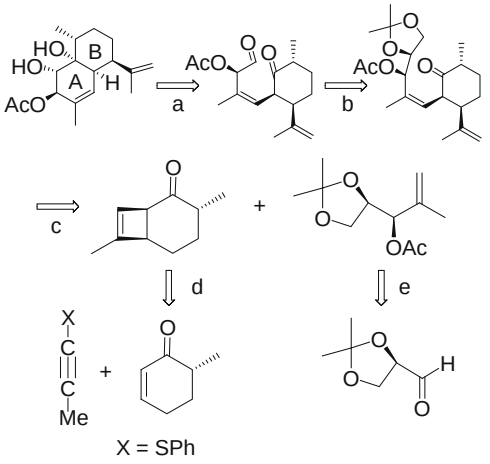


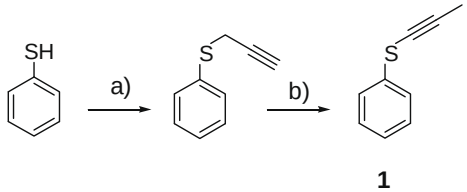
Scheme 1. Retrosynthetic analysis of the terpenoid core of CJ-12662 and CJ-12663.

phenyl-1-propynyl sulfide (X = PhS) as acetylene partner to ensure (a) the activation of the triple bond, (b) the control of the regioselectivity of the cycloaddition, (c) an easy replacement of the X substituent by hydrogen. Phenyl-1-propynyl sulfide **1** was prepared in two steps inspired by literature procedure (Scheme 2).[5]

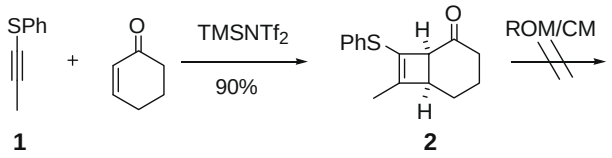
It was found that the cycloaddition of **1** with cyclohexenone took place readily in the presence of 10 mol % of $TMSNTf_2$ (Scheme 3). A single regio- and stereoisomer (**2**) was obtained in 90% yield after one hour at −40 °C.[6] Here again $TMSNTf_2$ was found superior[7] to TMSOTf and the corresponding Brönstedt acids HOTf and $HNTf_2$. These showed a much lower catalytic activity (reaction time > 1 day) and gave lower yields (45 to 65%).

We then explored the ring-opening metathesis/cross metathesis sequence by reacting adduct **2** with acrylonitrile, α-methyl acrylonitrile or 2-methylprop-2-enol in the presence of Grubbs and Hoveyda–Grubbs 2nd generation catalysts.[8,9] Compound **2** was recovered unaffected in each case (Scheme 3). Precedents for metathesis reaction with substrates carrying sulfide had however been reported.[10] Thus, the poor reactivity of **2** probably resulted from the high degree of substitution of the cyclobutene double bond. Therefore, the phenylsulfide group has to be removed before the ROM/CM reactions.

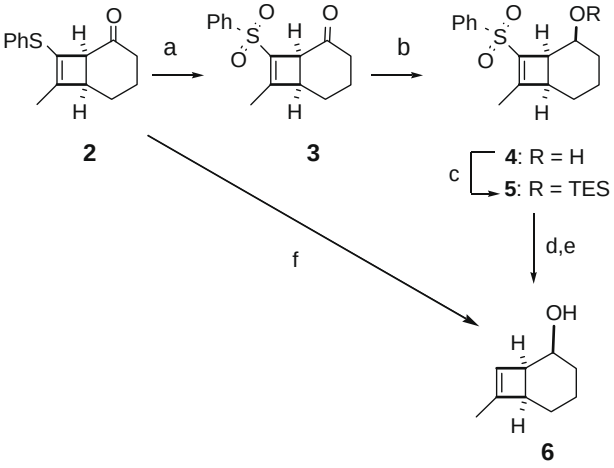
To this aim, oxidation of **2** with *m*-CPBA gave the corresponding phenylsulfone **3** in 72% yield (Scheme 4, step a). Treatment of **3** with activated magnesium turnings resulted in a slow reductive elimination of the phenylsulfone group with concomitant reduction of the ketone group to yield **6** (29%) as a mixture of epimeric alcohols.[11] A much better procedure consisted of a stereoselective reduction of the ketone group of crude **3** with sodium borohydride (step b) yielding a single alcohol **4** where the OH group is cis with respect to the cyclobutene ring (86% for two steps). The relative configuration of **4** has been confirmed by X-ray diffraction analysis (Fig. 2).[12]



Scheme 2. Reagents and conditions: (a) NaOH (1.7 equiv), propargyl bromide (1 equiv), TBAB (10 mol %), H_2O, 0 °C, 4 h; (b) *t*-BuOK (1.5 equiv), *t*-BuOH, 50 °C, 10 min (86%, 2 steps).



Scheme 3. Cycloaddition step.



Scheme 4. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 10 min; (b) $NaBH_4$, MeOH, −40 °C, 1 h; (c) TESCl, imidazole, CH_2Cl_2, 0 °C, rt, 12 h (87% for 3 steps); (d) activated Mg, MeOH, 50 °C, 1 h; (e) TBAF, THF, 2 h (91% for 2 steps); (f) *steps (a), (b) and (d) sequentially performed without purification of any intermediate*.

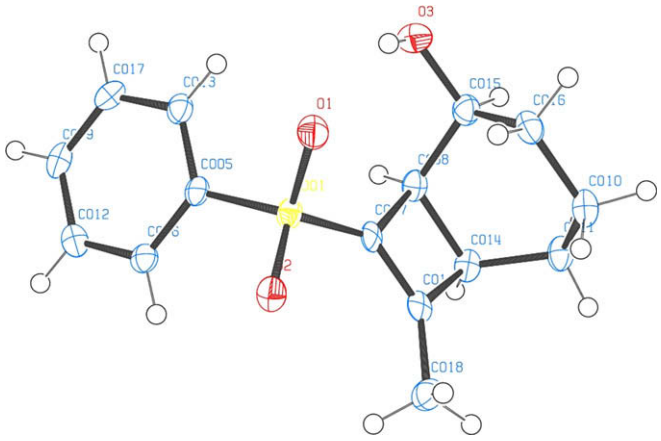
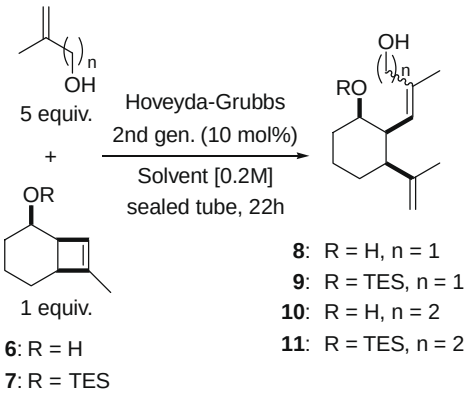


Figure 2. Ortep drawing of **4**.

Subsequent removal of the phenyl sulfone with activated magnesium turnings (step d) led to **6** but again only in poor yields. However, it was found that protection of the alcohol function (step c) followed by treatment of the resulting triethylsilyl ether **5** with activated magnesium turnings in methanol at 50 °C (step d) gave the target alcohol **6** after desilylation with tetrabutylammonium fluoride (step e). Optimization of this reaction sequence (Scheme 4, step f) led to a 70% yield for the synthesis of diastereomerically pure **6** from **2** *without purification of any intermediate.*

The ring opening metathesis of unsubstituted and monosubstituted double bonds of cyclobutenes followed by cross-metathesis with unsubstituted terminal olefins has been extensively studied by Snapper et al.[13] The factors effecting regioselectivity of the ring opening and the stereoselectivity of the formation of the new double bond have been studied in detail, and have shown to be depen-



Scheme 5. Tandem ring opening metathesis/cross metathesis reactions.

dant on the nature and degree of substitution of the cyclobutene double bond as well as that of the olefin partner. Further examples of the ROM/CM sequences have been reported by the groups of Harrity[14] and Szeimies.[15] To the best of our knowledge the tandem ROM/CM of a monosubstituted cyclobutene double bond with a 1,1-disubstituted olefin has not been described.[16]

Fivefold excesses of 2-methyl-2-propenol were reacted with compound **6** or the corresponding triethylsilyl ether **7** in the presence of 10 mol % of Hoveyda–Grubbs 2nd generation catalyst (Scheme 5, Table 1).[17] In all cases the reactions were totally regioselective but, the stereoselectivity was poor in all but one case. Stereoisomers *Z*-**8** (the required isomer for pinacol coupling) and *E*-**8** were separated by chromatography over silica gel and were recrystallized from chloroform.[12] The structure and configuration of both isomers were confirmed by a single-crystal X-ray diffraction analysis (Figs. 3 and 4).

Examination of Table 1 shows that both free alcohol **6** and the corresponding TES ether **7** gave similar results (entries a and b). Increasing the temperature led to a lower yield but a slightly better stereoselectivity in favour of the undesired isomer *E*-**8** (entry c). The best yields were obtained when the reaction was conducted at room temperature but the stereoselectivity was not improved (entry d). Interestingly 3-methyl-3-butenol didn't react at room temperature, extended reaction time led to partial decomposition of cyclobutene **6** (entry g). At 60 °C a mixture of isomers was obtained in moderate yield (entry f). Surprisingly, *E*-stereoselectivity was observed for the ROM/CM of **7** with 3-methyl-3-butenol, but yields dramatically dropped (entry e).

The above results are very promising in terms of implementing steps c and d of our retrosynthetic scheme (Scheme 1). In summary, we have developed a simple synthetic protocol for the attachment of the two cis-related carbon chains using a [2+2] cycloaddition to an enone. This should be applicable to a wide diversity of cyclic enones. The ROM/CM step is regiospecific but suffers from a poor stereoselectivity. However, in our model experiments, yields were high and after chromatographic separation, the desired (*Z*) isomer could be obtained in 42% yield.

Table 1
ROM/CM of compound **6** and **7**

Entry	R	*n*	Solvent	Temp (°C)[b]	Yield (%)	*Z*/*E* (NMR)
a	TES	1	DCM	60	60 (**9**)	1/1
b	H	1	DCM	60	47 (**8**)	1/1
c	H	1	DCE	90	40 (**8**)	1/2
d	H	1	DCM	rt	85 (**8**)	1/1
e[a]	TES	2	DCM	60	15(**11**)	<1/20
f	H	2	DCM	60	31(**10**)	1/3
g	H	2	DCM	rt	no reaction	

[a] 15 mol % HG2nd were used.
[b] Reaction performed in sealed tube.

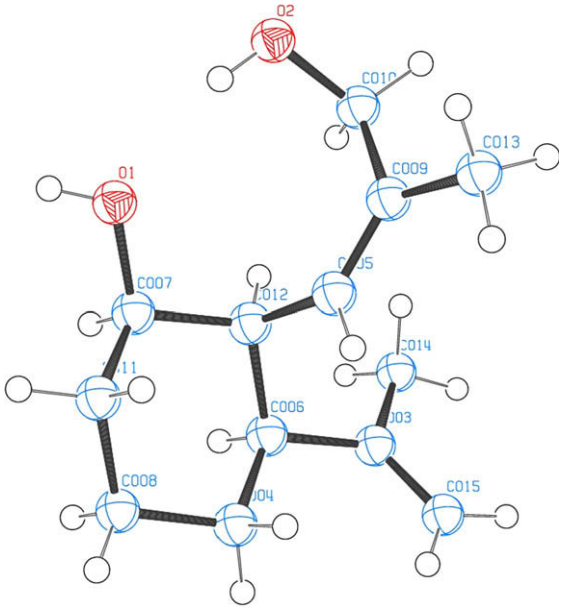


Figure 3. Ortep drawing of ***Z*-8**.

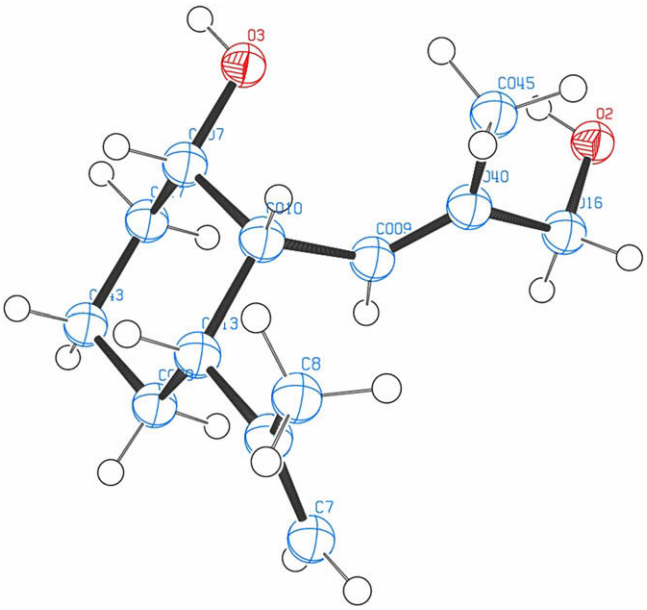


Figure 4. Ortep drawing of ***E*-8**.

Acknowledgments

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6. *Procedure for [2+2] cycloaddition for the synthesis of* **2**: Allyltrimethylsilane (37 μL, 0.23 mmol, 0.12 equiv) was added at room temperature to a 0.5 M solution of $HNTf_2$ in CH_2Cl_2 (390 μL, 0.194 mmol, 0.1 equiv) (Aldrich, cat. no. 15199) placed in a dried Schlenk tube under argon atmosphere. After 20 min, the mixture was diluted with 9.7 mL of anhydrous CH_2Cl_2 (0.2 M) and cooled down to −40 °C. Subsequently, cyclohex-2-en-1-one (188 μL, 1.94 mmol, 1 equiv) was added dropwise and was followed after 10 min by phenyl-1-propynyl sulfide **1** (0.575 g, 3.88 mmol, 2 equiv), and reaction was continued 1 h at −40 °C. After completion, monitored by TLC, the reaction mixture was diluted with CH_2Cl_2 (10 mL), quenched with saturated solution of $NaHCO_3$ (25 mL) at −40 °C, and next moved to room temperature and stirred for 30 min. The two layers were separated, and aqueous phase was extracted three times with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO_4, then filtrated and concentrated under vacuum. The crude compound was purified by flash chromatography using PE/EE: 20/1, 15/1, 10/1, 5/1 then 1/1 as eluent to give 0.429 g of the desired cycloadduct **2** as a pale yellow oil (90% yield). Pure 1-propynyl-phenylsulfide **1** (161 mg, 28%) was recovered. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.39 (d, J = 7.2 Hz, 2H, $H_{Ar\text{-}ortho}$), 7.33 (t, J = 7.2 Hz, 2H, $H_{Ar\text{-}meta}$), 7.26 (d, J = 7.2 Hz, 1H, $H_{Ar\text{-}para}$), 3.38 (br s, 1H, C*H*C=O), 3.28 (br s, 1H, C*H*CMe), 2.34 (m, 1H, part of CH_2C=O), 2.14–1.96 (m, 3H, part of CH_2C=O and CH_2CHCMe), 1.82–1.69 (m, 5H, CH_2CH_2C=O and CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 208.9 (C=O), 158.2 (=CMe), 135.7 (=CS), 132.0 ($C_{Ar\text{-}ipso}$), 130.8 ($C_{Ar\text{-}meta}$), 128.5 ($C_{Ar\text{-}ortho}$), 127.5 ($C_{Ar\text{-}para}$), 56.5 (CHC=O), 44.8 (CHCMe), 41.2 (CH_2C=O), 25.5 (CH_2CHCMe), 19.4 (CH_2CH_2C=O), 13.6 (CH_3); full assignment based on 2D NMR experiments (HMQC, HMBC); HRMS (MS ES+, Na) Calcd, for $C_{15}H_{17}OS$: 245.1000, found: 245.1010, Δ = 4 ppm.
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12. Crystallographic data (excluding structure factors) for compounds **4**, ***Z*-8** and ***E*-8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. 719864, 719863 and 719862, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
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17. *Procedure for the synthesis of* **8**: To a dried, sealed tube under argon atmosphere cyclobutene **6** (397 mg, 2.87 mmol, 1 equiv), anhydrous CH_2Cl_2 (14.35 mL, 0.2 M) and 2-methyl-2-propenol (1.21 mL, 14.35 mmol, 5 equiv) were introduced and the reaction mixture was degassed by bubbling a moderate stream of argon. Subsequently, Hoveyda–Grubbs 2nd generation catalyst (180 mg, 0.28 mmol, 0.1 equiv) as a CH_2Cl_2 solution was added and reaction mixture was stirred at room temperature for 22 h. After completion of the reaction, monitored by TLC, ethyl vinyl ether (2.14 mL, 22.4 mmol, 80 equiv/catalyst) was added and stirring was continued at room temperature for 30 min. Then mixture was concentrated under vacuum and dissolved again in CH_2Cl_2 (100 mL, 0.03 M) followed by addition of methanol solution of isocyanide potassium salt[18] (152 mg, 1.23 mmol, 4.4 equiv/catalyst, in 6 mL of methanol). After stirring at room temperature for 30 min. mixture was concentrated under vacuum, triturated three times with methanol and filtrated. The methanol extracts were combined, concentrated and finally purified by chromatography over silica gel using CH_2Cl_2/acetone = 8/1; 5:1 then 1:1 as eluent. The two stereoisomers *E*-**8** and *Z*-**8** were isolated respectively with 43% and 42% yield. A side-product, resulting from ROM/CM reaction between the cyclobutene **6** and the aromatic ligand of catalyst, was isolated with 10% yield. ***Z*-8**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.28 (d, J = 10.8 Hz, 1H, =C*H*), 4.72 (s, 1H, part of $=CH_2$), 4.61 (s, 1H, part of $=CH_2$), 4.24 (d, J = 11.7 Hz, 1H, part of C*H*$_2$OH), 3.78–3.70 (overlapped d, J = 11.4 Hz, part of C*H*$_2$OH and m, 1H, C*H*OH), 3.15–3.09 (m, 1H, C*H*CHOH), 2.73 (br s, 2H, 2*O*H*), 2.09 (m, 1H, C*H*C=CH_2), 1.85 (s, 3H, C*H*$_3$CCH$_2$OH), 1.65 (s, 3H, C*H*$_3$C=CH_2), 1.54–1.24 (m, 6H, $CH_2CH_2CH_2$CHOH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.3 (C=CH_2), 140.1 (=CCH_2OH), 122.6 (C=C*H*), 109.7 (C=CH_2), 72.8 (CHOH), 61.4 (CH_2OH), 46.1 (CHCHOH), 41.8 (CHC=CH_2), 30.6 (CH_2CHOH), 23.9 (C*H*$_2$CHC=CH_2), 23.8 (CH_2CH_2CHOH), 23.4 (CH_3C=CH_2), 22.1 (CH_3C=CH); full assignment based on 2D NMR experiments (HMQC, HMBC); HRMS (MS ES+, Na) calcd, for $C_{13}H_{22}O_2Na$: 233.1517, found: 233.1518, Δ = 0.2 ppm. ***E*-8**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.39 (d, J = 10.8 Hz, 1H, =C*H*), 4.69 (s, 1H, part of $=CH_2$), 4.57 (s, 1H, part of $=CH_2$), 3.98 (s, 2H, C*H*$_2$OH), 3.70 (m, 1H, C*H*OH), 3.09 (m, 1H, C*H*CHOH), 2.57 (br s, 1H, O*H*), 2.21 (br s, 1H, O*H*), 2.11 (br s, 1H, C*H*C=CH_2), 1.70 (s, 3H, C*H*$_3$C=CH_2), 1.66 (s, 3H, C*H*$_3$C=CH), 1.51–1.33 (m, 6H, $CH_2CH_2CH_2$CHOH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.4 (C=CH_2), 140.6 (=CCH_2OH), 119.8 (C=C*H*), 109.5 (C=CH_2), 73.6 (CHOH), 69.0 (CH_2OH), 46.4 (CHCHOH), 42.1 (CHC=CH_2), 30.5 (CH_2CHOH), 24.1 (CH_2CHC=CH_2), 24.0 (CH_2CH_2CHOH), 22.2 (CH_3C=CH_2), 14.5 (C*H*$_3$C=CH); full assignment based on 2D NMR experiments (HMQC, HMBC); HRMS (MS ES+, Na) calcd, for $C_{13}H_{22}O_2Na$: 233.1517, found: 233.1508, Δ = 4.1 ppm.
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