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Synthesis of highly substituted 2,6-*anti*-configured tetrahydropyrans. First steps towards an efficient access to amphidinol 3 ring system

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Abstract—Highly functionalised and polysubstituted tetrahydropyrans, akin to the middle core of the amphidinols, can be efficiently synthesised, with full stereocontrol and in good yields, using as key steps an *anti*-allylation reaction coupled with an intramolecular Sakurai cyclisation. Three approaches were devised in order to reach a broad range of substitution patterns.

Marine dinoflagellates are a rich source of natural products endowed with diverse structures and highly specific bioactivity.[1] Among these cyclic polyketides, amphidinols are unique metabolites, exhibiting high haemolytic and antifungal properties. The first member of this family was isolated by Yasumoto in 1991[2] and new derivatives are continuously being identified.[3] The relative and absolute stereochemistry of amphidinol 3 **1** has recently been elucidated through an elegant combination of spectroscopic analysis and degradation studies[4] (Fig. 1).

The challenging complexity of this structure lies in two main parts: the presence of two similarly substituted and *anti*-configured tetrahydropyrans, constituting the AB ring system, and the highly oxygenated northern side chain. Recently, Cossy and Bouzbouz reported[5] the preparation of the C_1–C_{14} part of amphidinol 3 **1**. However, to the best of our knowledge, no total synthesis of amphidinol 3 has yet been described. In this communication, we wish to present the successful implementation of a concise and flexible methodology for the rapid assembly of the fully functionalised tetrahydropyran fragments of **1**.

We have previously shown[6] that enantiomerically pure *syn–anti* and *syn–syn* configured triol units such as **4** and **5** could be synthesised efficiently by the $SnCl_4$-mediated allylation of chiral α-benzyloxyaldehydes **3** with the uniquely functionalised allylstannane **2**. Remarkably,

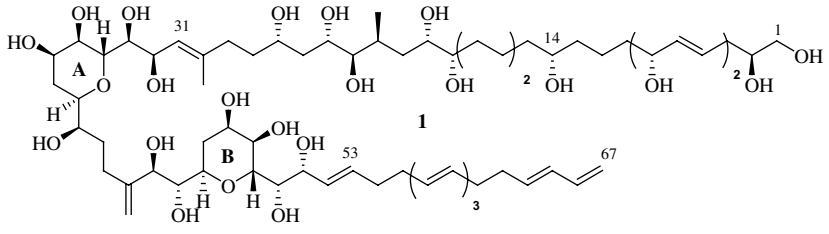

Figure 1. Amphidinol 3.

Keywords: Tetrahydropyrans; Amphidinols; Sakurai reaction; Allylation; Tin.
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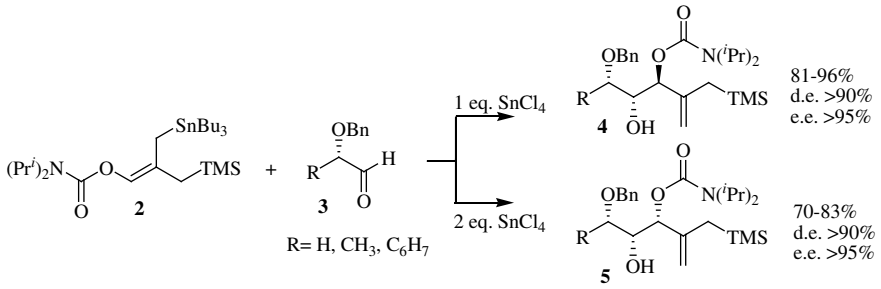


Figure 2.

the stereochemistry of these adducts was governed solely by the amount of Lewis acid employed (Fig. 2).

The resulting structures possess a stereodefined polyoxygenated triad as present in rings A and B of the amphidinols. Our efforts therefore focused on the subsequent transformation of adducts **4** and **5** into these important subunits. Acylation of alcohol **4** provided the corresponding, enantiomerically pure, acetate **6** in 85% yield (Fig. 3).

Unfortunately, numerous attempts at functionalising the allylsilane residue of **6** met with little success. Either no reaction was observed or desilylation took place. Interestingly, treatment of **6** with trimethylorthoformate[7] gave the β,γ-unsaturated acetal **7a** in 50% yield. Employing the more strained 2-methoxy 1,3-dioxolane afforded, in the presence of zinc dichloride etherate, adduct **7b** in up to 96% yield.

Various Lewis acids were then screened in order to shorten the reaction time and improve this process. Strong Lewis acids such as $SnCl_4$, $TiCl_4$ or $TiCp_2(OTf)_2$ led mainly to desilylation of the starting material and pure $ZnCl_2$ proved to be totally ineffective. A major breakthrough was observed when the unprotected compound **4** was submitted to this condensation reaction. In the presence of an orthoester and zinc dichloride etherate, allylsilane **4** unexpectedly generated the diastereoisomeric cyclic acetals **8** and **9** (*syn*:*anti* = 3:1) in excellent overall yield[8] (Fig. 4).

It is noteworthy that only the cyclic acetal, bearing a methoxy group, is obtained even when 2-methoxy-1,3-dioxolane is employed. It is assumed that this sequence proceeds via an initial transetherification reaction, leading to **10**, followed by the generation of the oxonium cation **11** and its subsequent intramolecular capture by the pendant allylsilane residue.

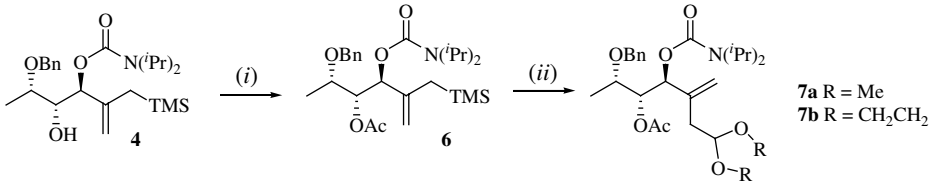


Figure 3. Reagents and conditions: (i) Ac_2O, pyridine, $DMAP_{cat}$ (85%); (ii) $(CH_3O)_3CH$, $ZnCl_2{\cdot}Et_2O$, $SnCl_4$, DCM, rt (50%) or 2-methoxy-1,3 dioxolane, $ZnCl_2{\cdot}Et_2O$, DCM, reflux (96%).

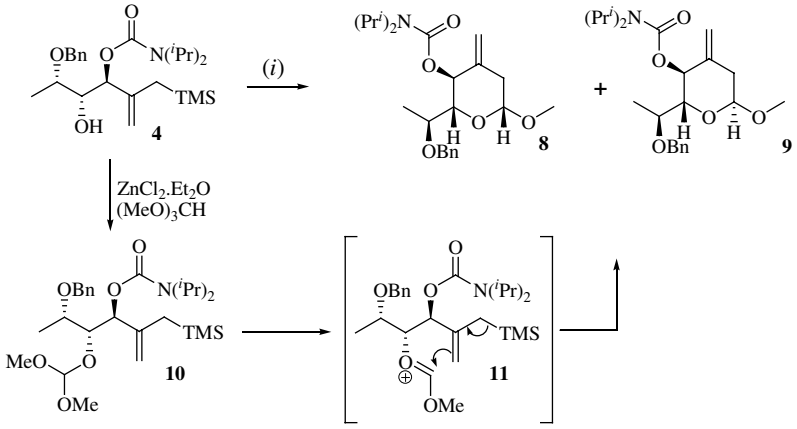
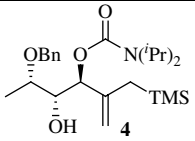
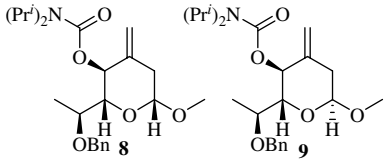
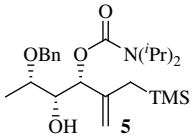
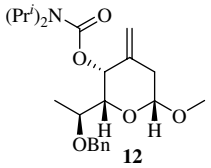
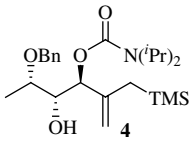
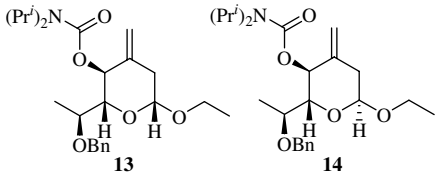


Figure 4. Reagents and conditions: (i) 2-methoxy-1,3-dioxolane, $ZnCl_2{\cdot}Et_2O$, DCM, reflux (93%) *or* $(MeO)_3CH$, $ZnCl_2{\cdot}Et_2O$, DCM, reflux (96%).

Table 1. Preparation of cyclic acetals

Entry	Allylsilane	Products[a]	Yield[b] (%)
1	 **4**	 **8** **9**	96[c]
2	 **5**	 **12**	83[c]
3	 **4**	 **13** **14**	95[d]

[a] Enantiomerically pure.
[b] Isolated yields.
[c] Conditions: $(MeO)_3CH$, $ZnCl_2{\cdot}Et_2O$, DCM.
[d] Conditions: $(EtO)_3CH$, $ZnCl_2{\cdot}Et_2O$, DCM.

The *syn–syn* isomer **5** was also submitted to these conditions and afforded exclusively the *syn*-diastereoisomer **12** in 83% yield. Finally, the use of triethylorthoformate led smoothly to the ethoxy-containing cyclic acetals **13** and **14** (Table 1).

In order to broaden the scope of this methodology, several other cyclic acetals were prepared, according to efficient and connective procedures previously developed in this laboratory.[9] Thus, treatment of allylselenide **15** with 1 equiv of *n*-BuLi, followed by the addition of an aldehyde, afforded the substituted allylsilanes **16** and **17** bearing an unprotected homoallylic alcohol function (Fig. 5).

Applying our optimised conditions to these compounds produced the desired cyclic acetals **18** and **19** in good to excellent yields (79–99%). With the aim of introducing

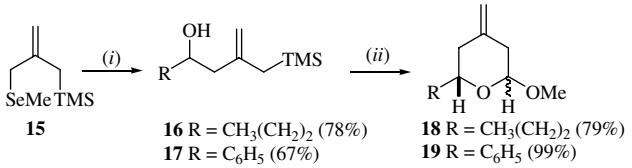


Figure 5. Reagents and conditions: (i) *n*-BuLi, RCHO, THF, −78 °C; (ii) $(MeO)_3CH$, $ZnCl_2{\cdot}Et_2O$, DCM, reflux.

stereoselectively, an oxygen-containing substituent in the final pyran ring system and hence access regiocomplementary structures, we took advantage of the Et_2AlCl-promoted ene reaction of allylsilane **20**.[10] Thus, condensation of aldehyde **21** with **20** gave the expected ene adduct **22**, as a single double bond geometric isomer, in 73% yield. Addition of $ZnCl_2{\cdot}Et_2O$ and $(MeO)_3CH$ to homoallylic alcohol **22** led smoothly to the desired pyran derivative **23** in 66% yield (Fig. 6).

The last operation in this three-step synthesis of highly substituted pyrans involved the transformation of these acetals into the alkylated, 2,6-*anti*-configured, heterocycles. It is well known in the literature[11] that carbohydrate derivatives easily undergo alkylation, with a high preference for the axial isomer, in the presence of a Lewis acid and a soft nucleophilic agent. The most common procedure employs TMSOTf or $BF_3{\cdot}Et_2O$, as the Lewis acid, and allyltrimethylsilane as the alkylating agent. Accordingly, several acetals were submitted to these conditions.[12] In all cases, a single diastereoisomer possessing the 2,6-*anti* relationship was obtained, even when an epimeric mixture of substrates was initially engaged in the reaction. The results are displayed in Table 2.

Based solely upon spectroscopic data, the relative stereochemistry of these adducts proved to be difficult to

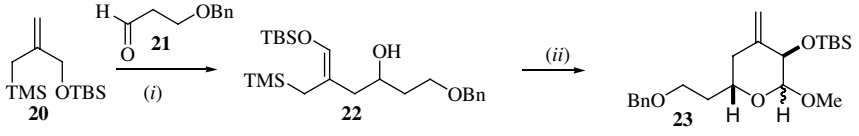
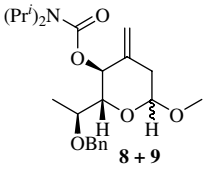
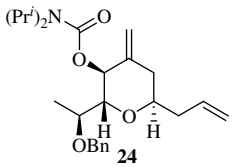
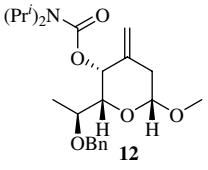
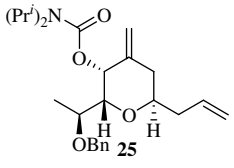
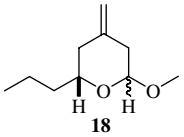
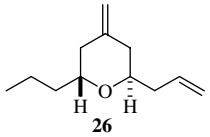
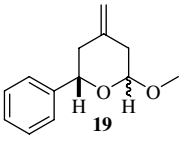
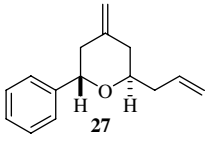
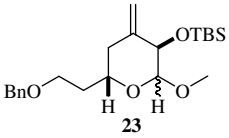
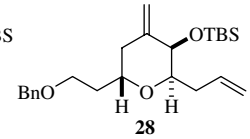


Figure 6. Reagents and conditions: (i) Et_2AlCl, Et_2O, −78 °C (73%); (ii) $(MeO)_3CH$, $ZnCl_2{\cdot}Et_2O$, DCM, reflux (66%).

Table 2. Allylation of cyclic acetals

Entry	Allylsilane	Products	Yield[a] (%)
1	 **8 + 9**	 **24**	82[b]
2	 **12**	 **25**	80[b]
3	 **18**	 **26**	69[c]
4	 **19**	 **27**	78[c]
5	 **23**	 **28**	81[c]

[a] Isolated yields.
[b] Enantiomerically pure.
[c] Racemic mixture.

establish reliably. To determine unambiguously their relative configuration, it was decided to synthesise the corresponding 2,6-*syn*-configured pyrans **29** and **30** and to compare them with **31** and **32**. The Intramolecular Silyl-Modified Sakurai (ISMS) reaction, a process well known to afford exclusively 2,6-*syn*-oxocenes,[13] was selected for that purpose. Accordingly, allylsilanes **4** and **5** were condensed with butyraldehyde, in the presence of $Bi(OTf)_3$, to give the desired 2,6-*syn*-pyrans **29** and **30** in good yields (Fig. 7).

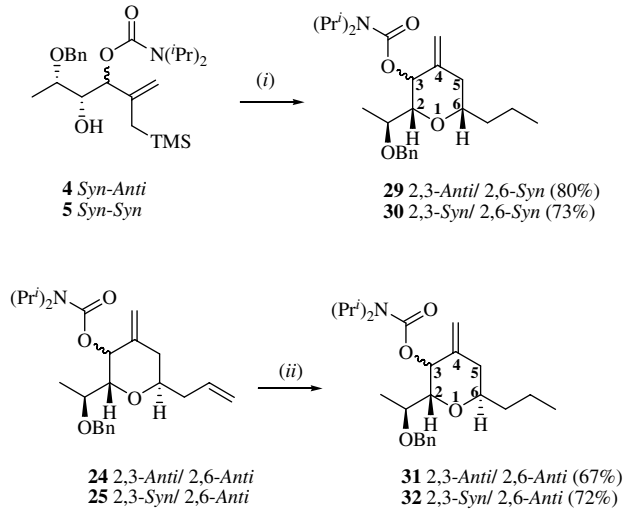


Figure 7. Reagents and conditions: (i) $Bi(OTf)_3$, butyraldehyde, THF, 0 °C; (*ii*) $TsNHNH_2$, AcOK, H_2O, reflux.

The terminal alkene of the 2,6-*anti*-configured pyrans **24** and **25** was chemoselectively reduced, using in situ generated diimide. Gratifyingly, both the NMR chemical shifts and the coupling constants of these compounds differed in the two series, confirming the proposed 2,6-*anti*-configuration for pyrans **31** and **32**. For example, the H_5–H_6 coupling constants were 4.6 and 5.5 Hz, in the case of the 2,6-*anti* isomer **31**, while the 2,6-*syn* isomer **29** exhibited coupling constants of 2.4 and 11.4 Hz.

At this stage, a single stereogenic centre was missing to mimic the Amphidinol 3 rings. The exocyclic double bond of acetals **8** and **9** was cleaved by ozonolysis (Fig. 8). In contrast to the ketone derived from the 2,6-*anti* acetal **9**, which was smoothly transformed into the desired axial product **35** by a variety of bulky reducing agents, the 2,6-*syn* acetal **8** always gave the equatorial alcohol, regardless of the reducing agent employed. Only DIBALH afforded a significant amount of **33**. After extensive optimisation of the reaction conditions, axial alcohol **33** could be obtained in 86% yield. The hydroxy function of **33** and **35** was next converted into an acetate group and the resulting acetals **34** and **36** were submitted to the allylation protocol.

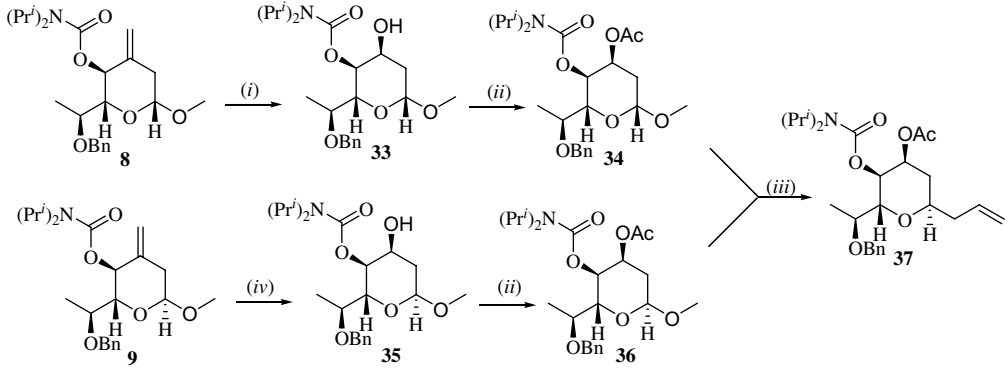


Figure 8. Reagents and conditions: (i) O_3, Me_2S, DCM, −78 °C then toluene, DIBALH, −40 °C (86%); (ii) Ac_2O, pyridine, $DMAP_{cat}$, rt (86%); (iii) TMSOTf, allylsilane, MeCN, −40 to 0 °C (92%); (iv) O_3, Me_2S, DCM, −78 °C then L-Selectride, THF, −78 °C (84%).

Gratifyingly, treatment of a mixture of **34** and **36** with allyltrimethylsilane, in the presence of TMSOTf, gave exclusively **37** in an exquisite 92% yield. This final product possesses all the functions and the correct stereochemical relationship present in rings A and B of the Amphidinols.

In summary, an efficient methodology for the rapid assembly of 2,6-*anti*-configured pyrans has been developed. This sequence tolerates a wide range of substituents and leads to a high diversity in the final adducts. The preparation of adduct **37**, embodying the correct functionalities and stereochemical relationships of amphidinol 3, has been accomplished with complete diastereo- and enantioselectivity. Current efforts are now dedicated towards linking these two rings and appending the two side chains of **3**. These results will be reported in due course.

Acknowledgements

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References and notes

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8. In a flame dried flask were mixed, at room temperature, trimethylorthoformate (250 μl, 242 mg, 2.29 mmol, 2 equiv) and 4.59 ml of a 1 M solution of $ZnCl_2$ in Et_2O (4.59 mmol, 4 equiv). The mixture was stirred for 15 min at 20 °C and then 1.14 ml of a 1 M solution of allylsilane **4** in dry DCM (1.14 mmol, 1 equiv) was added. After completion of the addition, the solution was heated to reflux and the reaction followed by TLC. When the reaction was complete, the mixture was cooled to 0 °C and a saturated aqueous solution of $NaHCO_3$ was added dropwise. An intense gas evolution was observed. The organic layer was separated and the aqueous layer extracted twice with DCM (20 ml). The organic layers were combined, dried over $MgSO_4$ and the solvents removed under vacuum. The crude product was purified by column chromatography on silica gel (PE 10/EA 1) to afford the desired product in pure form (445 mg, 96%); *anti*-isomer **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32–7.14 (5H, m), 5.50 (1H, d, J = 9.9 Hz), 4.83 (1 H, s), 4.80 (2H, s), 4.51 (1H, d, J = 11.7 Hz), 4.45 (1H, d, J = 11.7 Hz), 3.89 (2H, br m), 3.73 (1H, q, J = 6.3 Hz), 3.57 (1H, d, J = 9.6 Hz), 3.29 (3H, s), 2.61 (1H, d, J = 13.5 Hz), 2.42 (1H, d, J = 13.5 Hz), 1.26–1.06 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.64, 140.52, 138.08, 128.42, 128.18, 127.50, 108.25, 98.55, 74.55, 72.21, 71.87, 70.26, 54.90, 46.20–45.92, 38.99, 21.66–20.63, 16.04; MS (APCI) *m/z*: 374.1 (M−MeO); $[\alpha]_{20}^{D}$ +106.9 (*c* 1.0, CH_2Cl_2); *syn*-isomer **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32–7.14 (5H, m), 5.42 (1H, d, J = 9.6 Hz), 4.84 (1H, s), 4.73 (1H, s), 4.52 (1H, d, J = 10.2 Hz), 4.45 (1H, d, J = 10.2 Hz), 4.27 (1H, dd, J = 1.8; 13.5 Hz), 3.88 (2H, br m), 3.73 (1H, qd, J = 1.8; 9.6 Hz), 3.42 (3H, s), 3.26 (1H, dd, J = 1.8; 9.6 Hz), 2.54 (1H, dd, J = 2.4; 13.5 Hz), 2.38 (1H, t, J = 13.5 Hz), 1.26–1.06 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.41, 141.66, 138.25, 128.16, 128.10, 127.38, 108.59, 103.23, 79.59, 72.33, 71.89, 70.47, 56.30, 46.24–45.84, 40.59, 21.60, 20.76–20.58, 15.92; MS (APCI) *m/z*: 374.1 (M−MeO); $[\alpha]_{20}^{D}$ +14.5 (*c* 1.0, CH_2Cl_2).
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12. In a flame dried flask, a mixture of cyclic acetals **8** and **9** (100 mg, 0.24 mmol, 1 equiv) was dissolved in 4 ml of dry MeCN and cooled to −40 °C under argon. Allyltrimethylsilane (156 mg, 1.22 mmol, 5 equiv) was added and 1 equiv of freshly distilled TMSOTf (54.8 mg, 44 μl, 0.246 mmol) was added dropwise. The reaction mixture was allowed to reach 0 °C and the conversion was monitored by TLC. When completion was reached, the mixture was quenched with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted twice with DCM (20 ml). The organic layers were combined, dried over $MgSO_4$ and the solvents removed under vacuum. The crude was purified by column chromatography on silica gel (PE 10/EA 1) to afford the desired product **24** in pure form (84 mg, 82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29–7.17 (5H, m), 5.73 (1H, m), 5.22 (1H, d, J = 6.0 Hz), 5.02 (1H, d, J = 17.5 Hz), 4.98 (1H, d, J = 17.5 Hz), 4.88 (1H, s), 4.82 (1H, s), 4.53 (1H, d, J = 11.5 Hz), 4.39 (1H, d, J = 11.5 Hz), 3.99 (1H, br s), 3.86 (1H, m), 3.73 (1H, br s), 3.66 (1H, m), 3.59 (1H, t, J = 6.0 Hz), 2.36 (1H, dd, J = 4.3; 13.5 Hz), 2.32 (1H, m), 2.20 (1H, dd, J = 6.0 Hz; 13.5 Hz), 2.15 (1H, m), 1.18–1.12 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.54, 141.35, 138.70, 134.83, 128.42, 128.37, 127.68, 117.16, 111.19, 78.53, 72.37, 72.14, 71.87, 71.48, 46.69–45.63, 37.64, 37.13, 21.85–20.74, 16.35; MS (APCI) *m/z*: 416.0 ($M+H^+$).
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