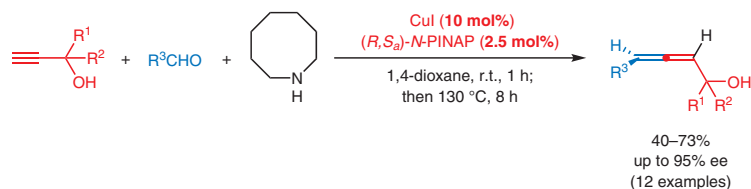


Copper(I) Iodide-Catalyzed Asymmetric Synthesis of Optically Active Tertiary α -Allenols

Qi Liu^{a,b}Tao Cao^{a,b}Yulin Han^{a,b}Xingguo Jiang^{a,b}Yang Tang^{a,b}Yizhan Zhaj^{a,b}Shengming Ma^{*a,c} 

^a State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. of China
masm@sioc.ac.cn

^b University of Chinese Academy of Sciences, Beijing 100049, P. R. of China

^c Research Center for Molecular Recognition and Synthesis, Department of Chemistry, Fudan University, 220 Handan Lu, Shanghai 200433, P. R. of China

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Abstract A facile CuI-catalyzed asymmetric synthesis of chiral tertiary α -allenols with up to 95% ee starting from common tertiary propargylic alcohols and aldehydes has been developed. The amount of chiral ligand used in this transformation can be as low as 2.5 mol%.

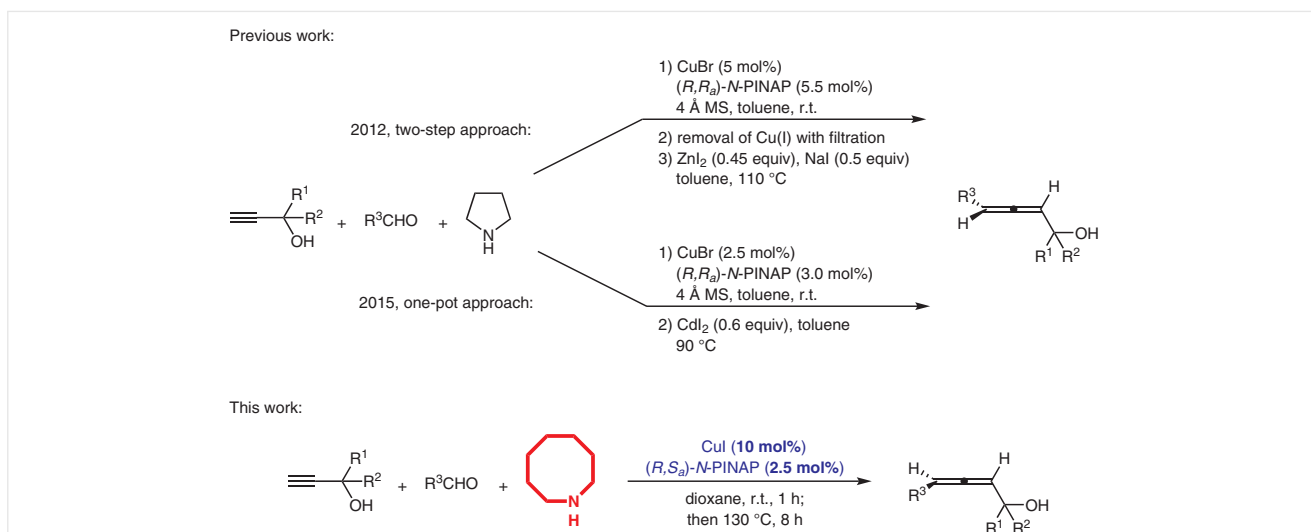
Key words copper catalysis, asymmetric synthesis, allenols, propargylic alcohols, aldehydes

Due to their unique structural properties, reactivities, and potential applications in medicine, allenes have attracted much attention from organic chemists, materials scientists, and pharmacists over the last few decades.^{1,2} A particular challenge in allene chemistry is to construct axially chiral allenes efficiently.³ Several strategies have been applied to achieve this goal.^{4,5}

In 2012, our group reported a two-step approach for the synthesis of optically active allenes from propargylic alcohols and aldehydes in which a catalytic amount of CuBr and a chiral 4-[1-(2-diphenylphosphanyl)naphthyl]-N-(1-phenylethyl)phthalazin-1-amine (*N*-PINAP) ligand⁶ are responsible for the highly enantioselective formation of a propargylic amine. After filtration to remove Cu(I), we used ZnI₂ (0.45 equiv) and NaI (0.5 equiv) to convert the optically active propargylic amine into an allene through a stereodefined *anti*-1,5-hydride shift (Scheme 1).^{5a} Later, we observed that CdI₂ works in harmony with CuBr to realize this transformation without filtration (Scheme 1).^{5b} However, both methods required a rather high loading of metal salts

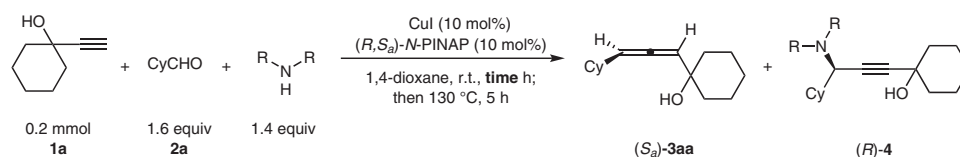
to promote the formation of allenes from the optically active propargylic amines generated in situ. Moreover, the stepwise addition of chemicals is not operationally friendly. Therefore, approaches to the enantioselective allenylation of terminal alkynes (EATA) that use a chiral catalyst operating in both steps are highly desired. Here, we report the realization of such a concept (Scheme 1).

On the basis of our previous observation that the dialkylamine played a vital role in the CuI-catalyzed synthesis of allenes from terminal alkynes and aldehydes,⁷ we reasoned that long-chain dialkylamines or structurally similar cyclic amines might be viable reactants for an enantioselective reactions of this type. After preliminary screening of a series of dialkylamines and cyclic amines, we were glad to find that the commercially available cyclic amine azocane was the most effective reactant in this EATA reaction (Table 1)⁸. When the reaction was carried out with propargylic alcohol (**1a**), 1.6 equivalents of cyclohexanal (**2a**), and 1.4 equiv of azocane with 10 mol% of CuI and 10 mol% of (*R,S*_a)-*N*-PINAP as the catalyst system at room temperature for 0.5 hours and then at 130 °C for five hours, the desired allenol (*S*)-**3aa** was formed in 76% yield and 86% ee (entry 7). Although a series of dialkylamines reacted smoothly to produce the corresponding propargylic amines, the second step to form the allene was not efficient (entries 1–3). In comparison, for cyclic amines, the second step became much easier on increasing the ring size from five to eight (entries 4–7). However, the yield of (*S*_a)-**3aa** decreased to 37% for azonane (entry 8), which was attributed to the fact that azonane is more similar to an open-chain dialkylamine.



Scheme 1 Enantioselective catalytic allenylation of terminal alkynes with aldehydes

Table 1 Amines Screened and Preliminary Results^a



| Entry | R, R | Time ^b (h) | Yield ^c (%) of (<i>S_a</i>)- 3aa | Yield ^c (%) of (<i>S_a</i>)- 4aa | ee ^d (%) of (<i>S_a</i>)- 3aa |
|-------|--|-----------------------|--|--|---|
| 1 | <i>i</i> -Bu, <i>i</i> -Bu | 24 | 6 | 78 | – ^e |
| 2 | Bu, Bu | 22 | 14 | 82 | – ^e |
| 3 | (±)-CH ₂ CH(Et)Bu, CH ₂ CH(Et)Bu | 18 | 4 | 76 | – ^e |
| 4 | –(CH ₂) ₄ – | 1 | 0 | 54 | – ^e |
| 5 | –(CH ₂) ₅ – | 2 | 10 | 84 | 76 |
| 6 | –(CH ₂) ₆ – | 1 | 35 | 52 | 76 |
| 7 | –(CH ₂) ₇ – | 0.5 | 76 | 12 | 86 |
| 8 | –(CH ₂) ₈ – | 1 | 37 | 65 | 88 |

^a The reaction was carried out on a 0.2 mmol scale in 1,4-dioxane (1.6 mL).

^b Reaction time for the first step.

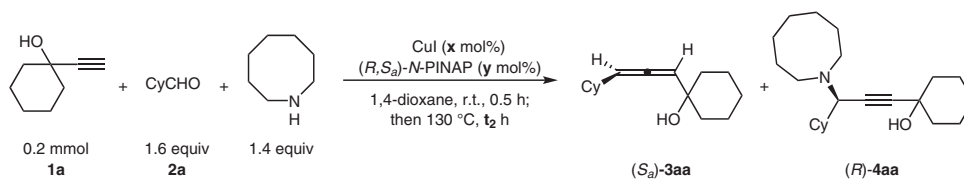
^c Determined by ¹H NMR analysis with CH₂Br₂ as the internal standard.

^d Determined by chiral HPLC analysis of the isolated product.

^e Not determined.

Encouraged by these preliminary results, we started to optimize the reaction conditions for the highly stereoselective formation of allene (*S*)-**3aa**. Surprisingly, we observed that the metal/ligand ratio had an obvious effect on the enantioselectivity.⁹ When the metal/ligand ratio was adjusted from 10:10 to 10:2.5, the ee value of (*S*)-**3aa** increased from 86% to 90% (Table 2, entries 1–4); however, a further reduction in the ratio of ligand led to a lower ee (entry 5). Increasing the ratio of CuI made no difference to the yield or the ee (entry 6). Furthermore, when the reaction temperature for the second step was lowered to 120 °C, the ee value

slightly increased, but the yield of (*S*)-**3aa** dropped to 59% (entry 7). When the reaction time for the second step was extended from 8 to 12 hours, the yield of (*R*)-**4aa** dropped from 6% to 4%, and the yield of (*S*)-**3aa** increased from 76% to 79%; however, the ee for (*S*)-**3aa** dropped from 90% to 87% (entry 8). After solvent screening, it was observed that 1,4-dioxane still provided the best yield and ee (entries 9–13). Thus, the optimized reaction conditions were as follows: a mixture of CuI (10 mol%), (*R,S_a*)-*N*-PINAP (2.5 mol%), propargylic alcohol (**1a**), aldehyde **2a** (1.6 equiv), and azocane (1.4 equiv) was stirred at room temperature in toluene

Table 2 Optimization of the Reaction Conditions^a

| Entry | x/y (mol%) | Solvent | t ₂ (h) | Yield ^b (%) of (S)-3aa | Yield ^b (%) of (R)-4aa | ee ^c (%) of (S)-3aa |
|----------------|------------|-------------------|--------------------|-----------------------------------|-----------------------------------|--------------------------------|
| 1 | 10/10 | 1,4-dioxane | 5 | 76 | 12 | 86 |
| 2 | 10/5 | 1,4-dioxane | 8 | 77 | 6 | 89 |
| 3 | 10/3.3 | 1,4-dioxane | 8 | 76 | 6 | 89 |
| 4 | 10/2.5 | 1,4-dioxane | 8 | 76 | 6 | 90 |
| 5 | 10/1.5 | 1,4-dioxane | 8 | 76 | 7 | 87 |
| 6 | 12.5/2.5 | 1,4-dioxane | 8 | 77 | 7 | 90 |
| 7 ^d | 10/2.5 | 1,4-dioxane | 8 | 59 | 22 | 91 |
| 8 | 10/2.5 | 1,4-dioxane | 12 | 79 | 4 | 87 |
| 9 | 10/2.5 | toluene | 8 | 62 | 8 | 85 |
| 10 | 10/2.5 | THF | 8 | 79 | 12 | 68 |
| 11 | 10/2.5 | MTBE | 8 | 38 | 54 | 87 |
| 12 | 10/2.5 | DCE | 8 | 21 | 60 | 67 |
| 13 | 10/2.5 | PhCF ₃ | 8 | 4 | 78 | – ^e |

^a The reaction was carried out on a 0.2 mmol scale in 1.6 mL of solvent.

^b Determined by ¹H NMR analysis with CH₂Br₂ as the internal standard.

^c Determined by chiral HPLC analysis of the isolated product.

^d The second-step reaction was carried out at 120 °C.

^e Not determined.

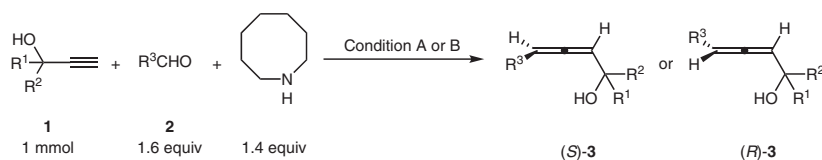
until the first step was complete (as monitored by TLC), and then the reaction tube was directly placed in an oil bath at 130 °C for the second step (entry 4).

The reaction was easily conducted on a 1 mmol scale (Table 3, entry 1). When (*R,R*)-*N*-PINAP was employed (Condition B), the enantiomer (*R*)-**3aa** was produced in a slightly higher ee (Table 3, entry 2). With the optimized conditions in hand, we started to investigate the scope of the reaction.¹⁰ In general, both cyclic and acyclic tertiary propargylic alcohols **1a–d** reacted with secondary alkyl aldehydes **2a–d** to give the corresponding allenols (*S*)-**3aa** to (*R*)-**3dc** in 40–73% yields and in 81–95% ee (entries 1–8). The enantioselectivity was sensitive to the R³ group of the aldehyde: increasing the steric bulk of the R³ group was beneficial to the enantiocontrol of the reaction (entries 7 and 8). The linear alkyl aldehyde **2e** also gave the corresponding allenol (*S*)-**3ce** in 53% yield, albeit with only 63% ee (entry 9). The first step of the reaction of aromatic aldehyde **2f** proved sluggish, and allene (*S*)-**3af** was obtained in 66% yield and with 65% ee (entry 10).

For the primary propargylic alcohol **1e** and the secondary propargylic alcohol **1f**, chiral α -allenols (*S*)-**3ea** and (*S*)-**3fa** were obtained in 52 and 69% yield, respectively; however, the ee values decreased to 60% and 41%, respectively (Scheme 2).

The absolute configurations of the allenols were assigned by comparison with authentic samples prepared by following the protocol described in a previous report⁵ and by applying the Lowe–Brewster rule.¹¹ A plausible model is proposed to predict the absolute configuration of the allenols (Scheme 3). First, the chiral alkynyl copper species (*R,S*)-**5**, generated in situ, reacts with the iminium intermediate **6**, also generated in situ from the aldehyde and azocane, to form the corresponding propargylic amine (*R*)-**4** enantioselectively.⁶ Subsequently Cu(I) coordinates to the C≡C triple bond with the assistance of the proximal hydroxy group to form complex **7**, which undergoes highly stereoselective *anti*-1,5-hydride transfer and *anti*- β -elimination to afford the corresponding allenol (*S*)-**3**.

In summary, we have developed a catalytic EATA reaction to synthesize optically active tertiary α -allenols from common tertiary propargylic alcohols and aldehydes by using only 10 mol% of CuI and 2.5 mol% of *N*-PINAP. The medium-sized cyclic amine azocane plays an important

Table 3 The Scope of the CuI/*N*-PINAP-catalyzed EATA Reaction^a

| entry | R ¹ , R ² (1) | R ³ (2) | Condition | Yield (%) of 3 | ee ^b (%) of 3 |
|-----------------|--|--|-----------|--------------------------------|---------------------------------|
| 1 | -(CH ₂) ₅ - (1a) | Cy (2a) | A | 72 [(<i>S</i>)- 3aa] | 90 |
| 2 | -(CH ₂) ₅ - (1a) | Cy (2a) | B | 73 [(<i>R</i>)- 3aa] | 91 |
| 3 | -(CH ₂) ₅ - (1a) | <i>i</i> -Pr (2b) | A | 54 [(<i>S</i>)- 3ab] | 92 |
| 4 | -(CH ₂) ₄ - (1b) | <i>i</i> -Pr (2b) | B | 45 [(<i>R</i>)- 3bb] | 95 |
| 5 | Me, Me (1c) | Cy (2a) | B | 65 [(<i>R</i>)- 3ca] | 84 |
| 6 | Me, Me (1c) | CHEt ₂ (2c) | A | 50 [(<i>S</i>)- 3cc] | 90 |
| 7 | Et, Et (1d) | cyclopentyl(2d) | B | 54 [(<i>R</i>)- 3dd] | 81 |
| 8 ^c | Et, Et (1d) | CHEt ₂ (2c) | B | 40 [(<i>R</i>)- 3dc] | 93 |
| 9 | Me, Me (1c) | (CH ₂) ₆ Me (2e) | A | 53 [(<i>S</i>)- 3ce] | 63 |
| 10 ^d | -(CH ₂) ₅ - (1a) | Ph (2f) | A | 66 [(<i>S</i>)- 3af] | 65 |

^a **Condition A:** **1** (1 mmol), **2** (1.6 equiv), azocane (1.4 equiv), CuI (10 mol%), (*R,S*)_o-*N*-PINAP (2.5 mol%), 1,4-dioxane (8 mL), r.t., 1 h, then 130 °C, 8 h; **Condition B:** As Condition A, but with ligand (*R,R*)_o-*N*-PINAP (2.5 mol%). The reaction was carried out on a 1 mmol scale in 1,4-dioxane (8 mL).

^b Determined by chiral HPLC analysis.

^c The reaction time for the first step was 24 h.

^d The reaction time for the first step was 48 h.

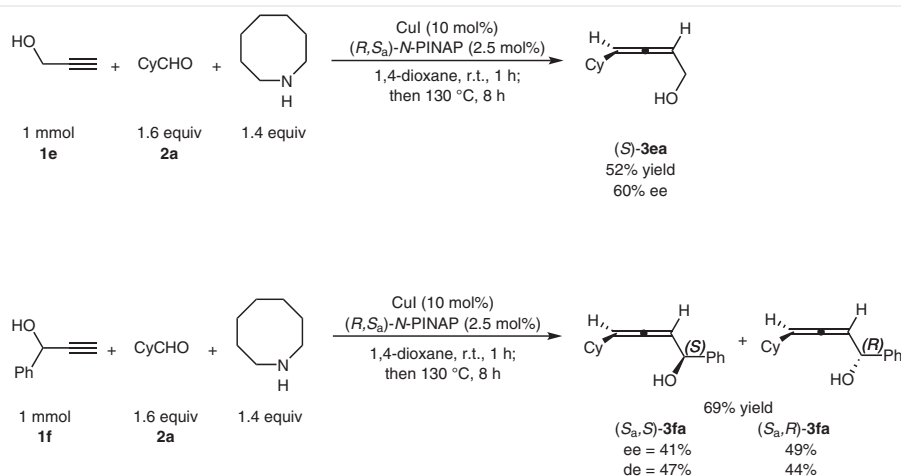
role in determining both the yield and enantioselectivity of this transformation. Another crucial factor affecting the stereoselectivity of the reaction is the metal/ligand ratio; however, it should be noted that the results for secondary terminal propargylic alcohols or normal terminal alkynes and aromatic/linear aliphatic aldehydes are still disappointing. Further studies, including the design of new ligands for such transformations, are being conducted in our laboratory.

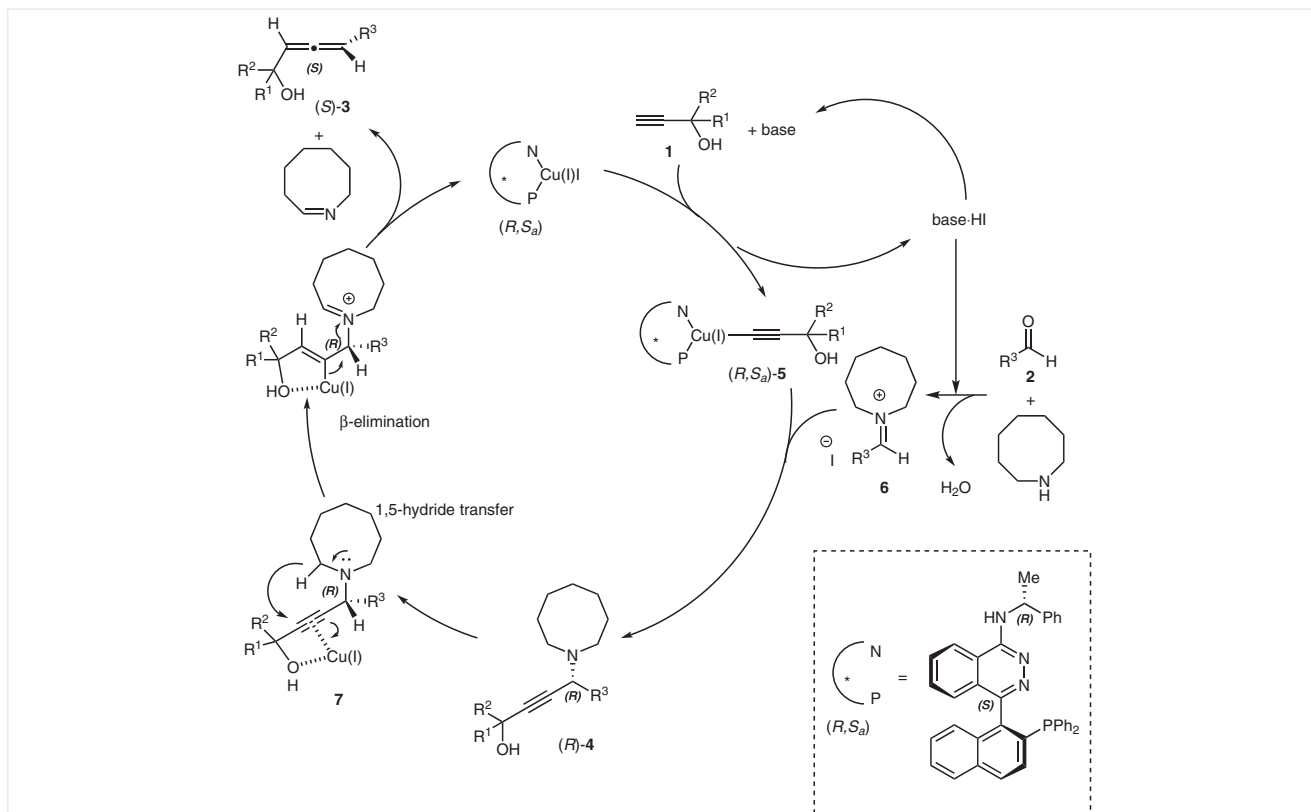
Funding Information

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We thank Mr. Yuchen Zhang in this group for reproducing the syntheses of (*R*)-**3ca**, (*S*)-**3cc**, and (*R*)-**3dc** presented in Table 3.

**Scheme 2** EATA Reaction with alkyne **1d** and **1e**



Scheme 3 Proposed mechanism and prediction of the absolute configuration of the allenols

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611641>.

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- (10) **1-[(1*S*)-4-Methylpenta-1,2-dien-1-yl]cyclohexanol [(*S*)-**3ab**]; **Typical Procedure**
A flame-dried Schlenk tube with a poly(tetrafluoroethylene) plug was charged with CuI (19.1 mg, 0.1 mmol), (*R,S*)₂-*N*-PINAP (14.1 mg, 0.025 mmol), and 1,4-dioxane (5 mL) under argon, and the mixture was stirred at r.t. for 30 min. Propargylic alcohol **1a** (123.7 mg, 1 mmol)/1,4-dioxane (1 mL), aldehyde **2b** (115.8 mg, 1.6 mmol)/1,4-dioxane (1 mL), and azocane (161.9 mg, 1.4 mmol)/1,4-dioxane (1 mL) were then added sequentially under argon. The mixture was then stirred at r.t. until the reaction was complete (TLC, ~1 h). The Schlenk tube was then placed in a preheated oil bath at 130 °C with stirring. After 8 h, the crude mixture was diluted with Et₂O (10 mL) and washed with 3 M aq HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated to give a residue that was purified by chromatography [silica gel, PE-EtOAc (20:1)] to give a liquid; yield: 97.0 mg (54%, 92% ee); $[\alpha]_{\text{D}}^{28} +80.8$ (*c* 1.005, CHCl₃). HPLC [Chiralcel AD-H column, hexane-*i*-PrOH (95:5), 0.5 mL/min, $\lambda = 214$ nm]: t_{R} (major) = 11.8 min; t_{R} (minor) = 10.9 min. IR (neat): 3343, 2958, 2927, 2859, 1961, 1598, 1494, 1463, 1446, 1410, 1380, 1360, 1345, 1318, 1297, 1246, 1192, 1176, 1163, 1146, 1112, 1088, 1058, 1038 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 5.38\text{--}5.30$ (m, 2 H, CH=C=CH), 2.41-2.27 (m, 1 H, CH), 1.79-1.41 (m, 10 H, protons from 5 x CH₂ + OH), 1.40-1.25 (m, 1 H, proton from CH₂), 1.030 (d, *J* = 6.8 Hz, 3 H, CH₃), 1.026 (d, *J* = 6.4 Hz, 3 H, CH₃). ¹³C NMR (100 MHz, CDCl₃): $\delta = 199.6, 102.3, 101.6, 70.5, 38.4, 38.3, 27.9, 25.5, 22.51, 22.47, 22.4$. MS (EI): *m/z* (%) = 180 (*M*⁺, 1.51), 99 (100). HRMS: *m/z* [*M*⁺] calcd for C₁₂H₂₀O: 180.1514; found: 180.1512.**
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