N-Heterocyclic Carbene Catalyzed Reaction of 2-(2-Aroylvinyl)cinnamaldehydes with α,β-Unsaturated Imines: An Efficient Method for the Stereoselective Synthesis of Highly Functionalized Indane Derivatives

Ming-Sheng Tang, Yuan Zhao, Ying Cheng*
College of Chemistry, Beijing Normal University, Beijing 100875, P. R. of China
Fax +86(10)58805558; E-mail: ycheng2@bnu.edu.cn
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Abstract: The NHC-catalyzed reaction of 2-(2-aroylvinyl)cinnamaldehydes with α,β-unsaturated imines was studied, which produced good yields of novel 3-aryl-9-[1,3-diaryl-3-(4-tolylsulfonylamido)allyl]-9,9a-dihydroinden[2,1-c]pyran-1(4aH)-ones with high diastereoselectivity. The products can be easily converted into different highly functionalized indane derivatives via simple operations. Thus, this work provides a simple and efficient method for the stereoselective synthesis of 1,2,3-trisubstituted indane derivatives.

Key words: N-heterocyclic carbene, catalysis, 2-(2-aroylvinyl)cinnamaldehyde, α,β-unsaturated imine, indane

A large number of indane derivatives are known to have a wide spectrum of biological activity. For example, indanes A substituted by 4-aminobutyl and benzyl show strong antibacterial activity (Figure 1).1 5-(5,6-Dichloroindan-1-yl)-1H-tetrazole (B) and 5-[(5,6-dichloroindan-1-yl)methyl]-1H-tetrazole (C) display significant analgesic and anti-inflammatory activity.2 The indanyl-substituted guanidinum D have been investigated as small-molecule HIV-1 entry inhibitors,3 and the sulfamides of 1-amino- and 2-aminoindanes E and F are potential carbonic anhydrase isoenzymes inhibitors.4 3-Amino-1-(indan-5-yl)propan-2-ol derivatives G exhibited blocking activity for Na+ channels, useful as potent sodium-channel blockers for the treatment of stroke victims.5 Various indane derivatives H derived from 7-aminoindan-4-ol are potent liver-selective thyroid hormone receptor β (TRβ) agonists for the treatment of dyslipidemia,6 while the 1-aminoindan-2-ol or 2-aminoindan-1-ol derivatives I and J have highly potent protein kinase C inhibitory activity.7 Due to their biological, pharmaceutical, and synthetic importance, interest in the synthesis of novel indane derivatives remains undiminished.2,8

Cascade reactions catalyzed by N-heterocyclic carbenes (NHCs) have received attention due to the resulting rapid generation of complex products.9 A few N-heterocyclic carbene catalyzed reactions have been reported to produce different indene or indane derivatives. For example, the cascade reactions of 2-formylcinnamates with imines, phthalaldehydes with imines, and phthalaldehydes with 3-aroylacrylates in the presence of NHC catalysts gave substituted indan-1-ones,10a-c while NHC-catalyzed reaction of 3,3′-(1,2-phenylene)bis(1-phenylpropanes) with aldehydes produced 1,2,3-trisubstituted indanes.10d Under catalysis by NHCs, the dimerization of o-formylchalones

Figure 1 Some bioactive indane derivatives
or 2-acrylamides, the reaction of 2-formylcinnamates, or the reaction of 2-formylchalcones with phthalaldehydes, afforded indene-spiro-indanone derivatives. On the other hand, the dimerization of phthalaldehydes catalyzed by a imidazole or triazole carbene produced dihydrosobenzofuran-spiro-indanones or indeno[2,1-c]indanone derivatives, respectively. NH$_2$-catalyzed self-reaction of 2-(2-arylviny1)cinnamaldehydes gave indeno[2,1-c]pyran-1-ones that were converted into indane-2-carboxylates and indane-2-carboxamides by the addition of alcohols or amines, and the oxidative NH$_2$-catalyzed cascade reaction between 2-(2-arylviny1)cinnamaldehydes and β-diketones produced 9-(β-diketones)indeno[2,1-c]pyran-1-ones. Our focus has mainly focused on NH$_2$-catalyzed reactions in recent years. We are interested in NH$_2$-catalyzed reactions of multifunctional reactants in terms of various possible reaction pathways and complex structures of products. We envisioned the reaction between α,β-unsaturated aldehydes linked with a Michael acceptor and α,β-unsaturated imines might have several different pathways. Thus, we studied the NH$_2$-catalyzed reaction of 2-(2-arylviny1)cinnamaldehydes with N-sulfonyl ketimines, which provided an efficient and stereoselective method for the synthesis of highly functionalized indane derivatives. We started this work by studying the reaction employing 2-(2-benzoylviny1)cinnamaldehyde (1a) and 1,3-diphenyl-N-tosylprop-2-en-1-imine (2a) as model substrates (Table 1). At ambient temperature and in dichloromethane, the reaction of 1a with 2a (1a:2a = 1:1.5) was initially catalyzed using 20 mol% of various triazole carbenes 3a–d that were generated from triazolium salts 3a–d with 1,8-diazabicyle[5.4.0]undec-7-ene (DBU). All these reactions produced product 4a, which was confirmed to be 9-[1,3-diphenyl-3-(4-tolylsulfonamido)allyl]-3-phenyl-9,9a-dihydroinden0[2,1-c]pyran-1(4H)-one (entries 1–4). Replacement of triazole carbene catalysts with thiazole carbene 3e′ or imidazole carbenes 3f′ and 3g′ resulted in no product or trace yields of product. Under the catalysis of triazole carbene 3d′, the reaction conditions were further optimized by varying temperature, solvent, and the base used to generate the carbene catalyst. It was found that decreasing reaction temperature to 0 °C improved the yield of 4a to 78%, however, further decreasing the temperature to −20 °C did not benefit the reaction, while elevating the temperature to the boiling point of dichloromethane led to the formation of product in a lower yield (entries 7–9). At 0 °C, the use of other solvents including benzene, aceton, acetonitrile, and tetrahydrofuran, or other bases like potassium tert-butoxide, sodium hydride, and cesium carbonate, all diminished the yield of product (entries 10–16). In addition to the major product 4a, a small amount of a minor product (below 10%) was detected in the crude product of most reactions by $^1$H NMR.

The scope of the reaction was then studied under the optimized conditions using α,β-unsaturated aldehydes 1 and α,β-unsaturated imines 2 that bear different substituents. It was found that the substituents of both reactants have a small influence on the reaction. As illustrated in Table 2, the reaction between 2-(2-arylviny1)cinnamaldehyde 1 and α,β-unsaturated imine 2 substituted by either electron-donating or electron-withdrawing groups on any of the four phenyl rings in 1 and 2, proceeded rapidly and efficiently to furnish products 4 in 69–84% yields in 20 minutes (entries 1–10, 13–15). Since the two phenyl groups of 2-(2-arylviny1)cinnamaldehydes 1 and the phenyl on the imine group of ketimines 2 are remote from the site of the reaction between 1 and 2, we considered that the steric effects of the substituents attached to these three phenyl rings could be ignored. Thus, we only examined the influence of the position of substituent attached to the phenyl group at C3 of ketimine 2. 3-(4-Methoxyphenyl)prop-2-en-1-imine 2c and 3-(3-methoxyphenyl)prop-2-en-1-imine 2e gave higher yields of products (71–79%) than that of 3-(2-methoxyphenyl)prop-2-en-1-imine 2f (63%) when they reacted with enal 1a (entries 9, 11, and 12). In addition to the product 4, the minor product 5 was detected in the crude products in 3–19% yields (ratios 4/5 = 4:1–21:1). Initially, we thought that compounds 5 were diastereomers of products 4. However, after the isolation of compound 5j, the spectroscopic characterization and single crystal X-ray diffraction analysis confirmed that 5j was 8-(benzoylmethyl)-3-(4-bromophenyl)-2-[phenyl(4-tolylsulfonamido)methylene]-3,3a,8,8a-tetrahydrocyclopenta[a]inden-1(2H)-one, which is derived from the intramolecular transformation of one diastereomer of the major product 4j. The minor products 5 were difficult to separate from the corresponding major products 4 by chromatography due to the fact that each pair of 4 and 5 has a similar polarity. Thus, with the exception of 5j which has the highest yield (19%) and the largest difference of polarity to 4j, other minor products 5 were not isolated. The byproducts 5 can be removed from the major products 4 by recrystallization.

To account for the formation of 3-aryl-9-[1,3-diary1-3-(4-tolylsulfonamido)allyl]indeno[2,1-c]pyran-1(4H)-ones 2 in 69–84% yields, proceeded rapidly and efficiently to furnish products 4 in 69–84% yields in 20 minutes (entries 1–10, 13–15). Since the two phenyl groups of 2-(2-arylviny1)cinnamaldehydes 1 and the phenyl on the imine group of ketimines 2 are remote from the site of the reaction between 1 and 2, we considered that the steric effects of the substituents attached to these three phenyl rings could be ignored. Thus, we only examined the influence of the position of substituent attached to the phenyl group at C3 of ketimine 2. 3-(4-Methoxyphenyl)prop-2-en-1-imine 2c and 3-(3-methoxyphenyl)prop-2-en-1-imine 2e gave higher yields of products (71–79%) than that of 3-(2-methoxyphenyl)prop-2-en-1-imine 2f (63%) when they reacted with enal 1a (entries 9, 11, and 12). In addition to the product 4, the minor product 5 was detected in the crude products in 3–19% yields (ratios 4/5 = 4:1–21:1). Initially, we thought that compounds 5 were diastereomers of products 4. However, after the isolation of compound 5j, the spectroscopic characterization and single crystal X-ray diffraction analysis confirmed that 5j was 8-(benzoylmethyl)-3-(4-bromophenyl)-2-[phenyl(4-tolylsulfonamido)methylene]-3,3a,8,8a-tetrahydrocyclopenta[a]inden-1(2H)-one, which is derived from the intramolecular transformation of one diastereomer of the major product 4j. The minor products 5 were difficult to separate from the corresponding major products 4 by chromatography due to the fact that each pair of 4 and 5 has a similar polarity. Thus, with the exception of 5j which has the highest yield (19%) and the largest difference of polarity to 4j, other minor products 5 were not isolated. The byproducts 5 can be removed from the major products 4 by recrystallization.

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lyl]inden[2,1-c]pyran-1-ones 4 are found in the reaction. The stereoselective formation of products 4 can be explained by the steric effects of substituents. In the formation of the indane ring of 4, the substituents attached to the stereocenters at C9 and C9a are arranged in a trans configuration to reduce the repulsion of substituents, while the two fused C4a and C9a stereocenters are in a cis configuration to avoid fused-ring strain. The minor cyclopenta[a]inden-1-one products 5 are derived from the isomerization of minor diastereomers 11 by the intramolecular addition of the enamine to the δ-lactone species of 11 under the catalysis of a base, such as triazole carbene or DBU. However, the major diastereomers 4 could not undergo such a transformation as the enamine and δ-lactone species of 4 are trans substituted on the indane ring.

The lactone moiety of indeno[2,1-c]pyran-1-ones are known to be easily cleaved by the addition of nucleophiles, such as alcohols or amines. Therefore, it would be possible to convert 9-[3-(sulfonamido)allyl]inden[2,1-c]pyran-1-ones 4 into various highly functionalized indane derivatives. To extend the applications of the current reaction in the synthesis of indane derivatives, the different transformations of 3-aryl-9-[1,3-diaryl-3-(tolyl-

Table 1  Optimization of the Reaction Conditions

<table>
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<tr>
<th>Entry</th>
<th>NHC precursor</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>Yield (%) of 4a</th>
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<td>DBU</td>
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<td>trace</td>
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<tr>
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<td>r.t.</td>
<td>5 h</td>
<td>19 a</td>
</tr>
<tr>
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<td>3c</td>
<td>DBU</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>5 h</td>
<td>21 a</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>DBU</td>
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<td>r.t.</td>
<td>20 min</td>
<td>66</td>
</tr>
<tr>
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<td>3e</td>
<td>DBU</td>
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<td>r.t.</td>
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<td>r.t.</td>
<td>8 h</td>
<td>– b</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
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<td>CH₂Cl₂</td>
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<td>8 h</td>
<td>– b</td>
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<tr>
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<td>0</td>
<td>2 h</td>
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- The enal 1a was not totally consumed.
- Not found.
sulfonamido)allyl]indeno[2,1-c]pyran-1-ones 4 were examined. For example, 4a was converted into methyl 1-(benzoyl methyl)-3-[1,3-diphenyl-3-(4-tolylsulfonamido)allyl]indane-2-carboxylate (14) in 82% yield on heating in refluxing methanol. At ambient temperature, the hydrolysis of 4a with aqueous 30% sodium hydroxide solution followed by saturated aqueous solution of ammonium chloride in tetrahydrofuran afforded 1-(benzoylmethyl)-3-(2-benzoyl-1-phenylethyl)indane-2-carboxylic acid (15) in 80% yield. Reduction of 4a with lithium aluminum hydride in tetrahydrofuran produced 9-[1,3-diphenyl-3-(4-tolylsulfonamido)allyl]-3-phenyl-1,4a,9,9a-tetrahydroindeno[2,1-c]pyran (16) in 70% yield (Scheme 2).

Enantioselective synthesis of 9-[3-(sulfonamido)allyl]indeno[2,1-c]pyran-1-ones 4 was also attempted using chiral triazole carbenes. As shown in Scheme 3, while chiral pyrrolo[2,1-c]triazole car bene 3h did not promoted the reaction of enal 1a with N-tosyl ketimine 2a, a small amount of product 4a (15%) was obtained from the reaction catalyzed by N-(pentafluorophenyl)hexahydroindeno[2,1-b]triazolo[3,4-c][1,4]oxazine carbene 3i. However, to our delight, under catalysis by N-phenylhexahydroinden o[2,1-b]triazolo[3,4-c][1,4]oxazine carbene 3j, the reaction of enal 1a with ketimine 2a provided 4a in 45% yield with high enantioselectivity (90% ee, absolute configuration of 4a was not determined.) (Scheme 3). This initial study on the asymmetric reaction of 2-(2-benzoylvinyl)cinnamaldehyde (1a) with N-tosyl ketimine 2a indi-

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<th>R3</th>
<th>R4</th>
<th>Yielda (%) Total</th>
<th>4b</th>
<th>5c</th>
<th>Ratio d 4/5</th>
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<td>83</td>
<td>4o: 74</td>
<td>5o: 9</td>
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* The isolated yields.
* The yields of 4 and 5 were calculated based on the ratios of 4/5 and the total yields of products.
* Except 5j, other minor products 5 were not isolated and characterized.
* The ratios of 4-5 were detected by 1H NMR on the crude products.
Scheme 1 The proposed mechanism for the formations of 3-aryl-9-[1,3-diaryl-3-(4-tolylsulfonamido)allyl]indeno[2,1-c]pyran-1-ones 4 and 8-(arylmethyl)-3-aryl-2-[aryl(4-tolylsulfonamido)methylene]-3,3a,8,8a-tetrahydrocyclopenta[a]inden-1(2H)-ones 5 from the reaction 2-(2-arylvinylic)cinamaldehydes 1 with 1,3-diaryl-N-tosylprop-2-en-1-imines 2

Scheme 2 The transformations of 9-[1,3-diphenyl-3-(4-tolylsulfonamido)allyl]-3-phenylindeno[2,1-c]pyran-1-one 4a

Scheme 3 Asymmetric reaction of 2-(2-benzoylvinyl)cinamaldehyde 1a with N-tosyl ketimine 2a catalyzed by chiral triazole carbene
cates that the enantioselective synthesis of 9-[3-(sulfonamido)allyl]indenophane-1,2-cpyran-1-ones 4 can be achieved using chiral triazole carbene \[3\] as the catalyst.

In summary, we have developed an efficient NHC-catalyzed reaction of 2-(4-aryvinyl)indenophane-1,2-cpyran-1-ones with high diastereoselectivity. Indane is a framework that is found in a large number of bioactive and pharmaceutically important molecules. This work provided unique indane derivatives that are amenable to further transformations.

Commercially available chemical reagents were used without further purification. Anhyd CHCl\(_3\) was prepared by distillation over P\(_2\)O\(_5\). Melting points are uncorrected. Petroleum ether = PE. \(^1\)H (400 or 500 MHz) and \(^13\)C NMR (100 or 125 MHz) were recorded in the indicated solvents using a Bruker instrument. IR spectra were recorded using an AVATAR 360 FT-IR spectrophotometer. Mass spectra were recorded on a Surveyor MS Plus (ESI) instrument. Column chromatography was performed using 200–300 mesh silica gel. The 2-(4-aryvinyl)indenophane-1,2-cpyran-1-ones were prepared according to literatures methods.

**NH-Catalyzed Reaction of 2-(4-Arylvinyl)indenophane-1 with 1,3-Diaryl-N-tosylprop-2-en-1-imines 2:** General Procedure

Under N\(_2\) atmosphere and at 0 °C, 2-(4-aryvinyl)indenophane-1 \((0.5 \text{ mmol})\), 1,3-diaryl-N-tosylprop-2-en-1-imines 2; General Procedure 1(4) was added, and the mixture was stirred for 10 min at 0 °C, and then DBU (0.5 mmol) was added into the mixture. The mixture was stirred at 0 °C for ca. 20–30 min until the enal had been consumed. After removal of molecular sieves and the solvent, the residue was further purified by recrystallization (n-hexane-CHCl\(_3\)).

**4(\(\text{S}^\text{a}\),\(\text{S}^\text{a}\),\(\text{S}^\text{a}\),\(\text{S}^\text{a}\))**

This product 4 was further purified by recrystallization (n-hexane-CHCl\(_3\)).

4(\(\text{S}^\text{a}\),\(\text{S}^\text{a}\),\(\text{S}^\text{a}\),\(\text{S}^\text{a}\))

White crystals; yield: 249 mg (0.39 mmol, 78%); mp 185–187 °C. IR: 3298, 1751, 1614 cm\(^{-1}\).

HRMS (ESI): \(m/z\) [M + H]+ calecd for C\(_{40}\)H\(_{34}\)NO\(_4\)S: 624.2209; found: 624.2218.

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IR: 3162, 1735, 1598 cm⁻¹.
White crystals; yield: 246 mg (0.35 mmol, 70%); mp 206–208 °C.
IR: 3347, 3282, 1749, 1598 cm⁻¹.
White crystals; yield: 229 mg (0.36 mmol, 71%); mp 146–147 °C.

ran-1(4a)
White crystals; yield: 235 mg (0.36 mmol, 72%); mp 180–181 °C.
(4-tolylsulfonamido)allyl]-9,9a-dihydroindeno[2,1-c]pyran-1(4H)-one (4f)
White crystals; yield: 261 mg (0.4 mmol, 79%); mp 191–192 °C.
ran-1(4a)
White crystals; yield: 245 mg (0.35 mmol, 70%); mp 164–165 °C.

HRMS (ESI): m/z [M + H⁺] caleđ for C₄₁H₃₆NO₅S: 654.2314; found: 654.2310.

(4aS,9S,9aS,1'R,R')-9-[1-(4-Methoxyphenyl)-3-phenyl-3-(4-tolylsulfonamido)allyl]-9,9a-dihydroindeno[2,1-c]pyran-1(4H)-one (4h)
White crystals; yield: 70 mg (0.1 mmol, 19%); mp 125–126 °C.
IR: 3436, 1687, 1650, 1570 cm⁻¹.
HRMS (ESI): m/z [M + H⁺] caleđ for C₄₉H₃₆BrNO₅S: 702.1314; found: 702.1309.

(3S,3aS,8R*,8aS*,Z)-8-(Benzoylmethyl)-3-(4-bromophenyl)-2-phenyl-4-tolylosulfonamido)methylene)-3,3a,8,8a-tetrahydrocyclopena[a]inden-1(2H)-one (5i)
White crystals; yield: 235 mg (0.36 mmol, 71%); mp 149–151 °C.
IR: 3281, 1744, 1598 cm⁻¹.
HRMS (ESI): m/z [M + H⁺] caleđ for C₄₉H₃₆BrNO₅S: 702.1314; found: 702.1309.

(4aS,9S,9aS,1'R,R')-9-[1-(3-Methoxyphenyl)-3-phenyl-3-(4-tolylsulfonamido)allyl]-9,9a-dihydroindeno[2,1-c]pyran-1(4H)-one (4i)
White crystals; yield: 261 mg (0.4 mmol, 79%); mp 191–192 °C.
IR: 3281, 1744, 1598 cm⁻¹.
HRMS (ESI): m/z [M + H⁺] caleđ for C₄₉H₃₆BrNO₅S: 702.1314; found: 702.1309.
1H NMR (500 MHz, acetone-\(d_6\)): \(\delta = 8.06\) (s, 1 H), 7.69 (d, \(J = 7.3\) Hz, 2 H), 7.55 (d, \(J = 6.2\) Hz, 2 H), 7.39 (d, \(J = 7.4\) Hz, 2 H), 7.37 (t, \(J = 7.2\) Hz, 1 H), 7.07 (d, \(J = 6.8\) Hz, 2 H), 7.00–7.05 (m, 4 H), 6.91 (d, \(J = 5.0\) Hz, 1 H), 6.20 (d, \(J = 10.6\) Hz, 1 H), 4.35 (t, \(J = 5.8\) Hz, 1 H), 4.19 (dd, \(J = 8.2, 5.1\) Hz, 1 H), 4.11 (dd, \(J = 10.4, 6.4\) Hz, 1 H), 3.91 (s, 3 H), 2.97 (dd, \(J = 8.4, 5.2\) Hz, 1 H), 2.28 (s, 3 H).

IR: 3173, 1737, 1605 cm\(^{-1}\).

**HRMS (ESI):** \(m/z\) [M + H\(^+\)] calec for C\(_{41}\)H\(_{36}\)NO\(_5\)S: 654.2314; found: 654.2313.

**Synthesis**

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**Methyl (1S,2R,3S,5R,9S)-1-(Benzoxymethyl)-3-(2-benzoyl-1-phenyl-3-(4-tolysulfonylamido)allyl)-3-phenyl-9,9a-dihydroindeno[2,1-c](pyran-1-one) (4a)

White crystals; yield: 236 mg (0.37 mmol, 74%); mp 168–169 °C.

IR: 3441, 1728, 1633, 1595 cm\(^{-1}\).

**HRMS (ESI):** \(m/z\) [M + Na\(^+\)] calec for C\(_{41}\)H\(_{35}\)NO\(_5\)SNa: 678.2285; found: 678.2271.
7.29 (t, J = 7.6 Hz, 2 H), 7.11–7.18 (m, 4 H), 7.05–7.09 (m, 4 H), 6.95 (d, J = 7.4 Hz, 1 H), 3.76–3.82 (m, 2 H), 3.72 (dd, J = 14.6, 7.7 Hz, 1 H), 3.46 (d, J = 6.0 Hz, 2 H), 3.28 (d, J = 8.1 Hz, 1 H), 3.26 (dd, J = 15.5, 8.2 Hz, 1 H), 3.17 (dd, J = 18.0, 6.1 Hz, 1 H).

C NMR (100 MHz, CDCl3): δ = 198.8, 195.7, 189.0, 144.3, 143.4, 141.2, 137.2, 136.9, 133.1, 133.0, 128.5, 128.3, 128.0, 127.5, 127.1, 126.8, 125.1, 123.4, 52.7, 50.4, 43.6, 41.9, 40.7, 39.8.


White crystals; yield: 207 mg (0.34 mmol, 70%); mp 108–110 °C.

The product (5 mL) under 0 °C. After extraction with CH2Cl2 (10 × 3 mL), the mixture was stirred at rt for ca. 1 h until 4a had been consumed. The reaction was quenched by the addition of 2 M aq HCl (5 mL) under 0 °C. After extraction with CH2Cl2 (10 × 3 mL), the product 16 was isolated by rapid column chromatography (silica gel, PE–EtOAc, 5:1).

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Supporting Information

for this article is available online at http://www.thieme-connect.com/ejournals/toe/synthesis. Included are copies of 1H NMR and 13C NMR spectra of products 4, 5j, 14, 15, 16, and the HPLC spectra of 4a.

References


(13) CCDC 956769 and 956770 (4a and 5j) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

