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An expeditious protocol for sesquiterpene-cored functionalized arenes from *S*-(−)-citronellal ☆

Atul Goel *, Deepti Verma

Division of Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow 226 001, India

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ABSTRACT

An expeditious straightforward synthesis of sesquiterpene-cored arenes functionalized with electron-withdrawing or electron-donating substituents is described and illustrated by Michael addition of *S*-(−)-citronellal on functionalized 2*H*-pyran-2-one in a single step at room temperature. The reaction was further generalized by synthesizing isoprenylated 9,10-dihydrophenanthrene-2-carbonitrile using 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitriles and *S*-(−)-citronellal under similar reaction conditions.

The monocyclic aromatic sesquiterpenes of the bisabolene family are an important class of natural products exhibiting a wide range of biological activities.[1] These scaffolds often possess a benzylic chiral centre carrying a methyl group at this position. Amongst several bisabolene sesquiterpenoids, the simplest *S*-(+)-curcumene has been isolated from rhizomes of *Curcuma aromatica* Salisb, and it is the active constituent of a large number of essential oils.[2] The phenolic sesquiterpene (+)-curcuphenol isolated from a marine sponge (*Epipolasis* and *Didiscus flavus*) showed gastric H,K-ATPase inhibitory and antitumor and antifungal activities.[3,4] Interestingly, its enantiomer, which has been isolated from the gorgonian coral *Pseudopterogorgia rigida*, exhibits antibacterial activity against *Staphylococcus aureus*.[4,5] Recently, natural dimers of curcuphenols displayed lipoxygenase inhibitory activities.[6] An isomeric xanthorrhizol exhibits antitumor activity, and it is used as traditional medicine in Indonesia.[7,8]

During our ongoing drug development programme, we became interested in uncovering the biological properties of functionally diverse curcumene-cored novel aromatic compounds. Although numerous interesting biological properties of these sesquiterpenoids have prompted considerable synthetic efforts to the targeted natural products, there is a surprising lack of flexible and donor–acceptor functional group tolerable general methods for sesquiterpene-cored aromatic compounds. Herein, we report an efficient and convenient route for the synthesis of sesquiterpene-cored functionalized arenes through a ring transformation reaction of 2*H*-pyran-2-ones or 5,6-dihydro-2-oxo-2*H*-benzo[*h*]chromene-3-carbonitriles using *S*-(−)-citronellal as a source of carbanion. The advantage of the procedure lies in the construction of a benzene ring with flexibility of substituent variations in a single step at room temperature.

Due to diverse biological activities[9] associated with this scaffold, numerous approaches have been adapted;[10] however, enantioselective methods remain sparse in the literature.[11] The synthetic methods include Grignard reaction of *p*-tolylmagnesium bromide with 6-methyl-3,5-heptadien-2-one;[11a] enzymatic resolution of racemic intermediates;[11b] the Mitsunobu reaction of synthetic equivalent of chiral 2-cyclopentenol followed by a concurrent retro-Diels–Alder reaction and Claisen rearrangement;[11c] baker's yeast reduction approach;[11d,e] sparteine-mediated lateral metallation-substitution reaction,[11f] from enantiomerically pure benzothiazine precursor via a stereoselective, intramolecular Michael addition reaction;[11g] highly stereoselective addition of aryllithium reagent to chiral α,β-unsaturated oxazolines;[11h] asymmetric hydrogen-esterification reaction[11i] and 1,4-conjugate addition of chiral citronellal to vinyl ketones followed by an intramolecular aldol condensation.[11j]

The newer approaches for the synthesis of bisabolene skeleton involve asymmetric hydrovinylation followed by Suzuki–Miyaura reaction,[12] the asymmetric conjugate addition using a enantiomerically pure sulfoxide as the chiral auxiliary,[13] chemoenzymatic route via lipase-catalyzed kinetic resolution process,[14] solvolysis of (4,5-*anti*)-4-aryl-5-tosyloxy-(2*E*)-hexenoate in water-saturated $MeNO_2$ based on 1,2-aryl migration via phenonium ion.[15]

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* Corresponding author at present address: Institut für Organische Chemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany. Tel.: +49 931 8885393; fax: +49 931 8884755.
E-mail addresses: agoel13@yahoo.com, goela@chemie.uni-wuerzburg.de (A. Goel).

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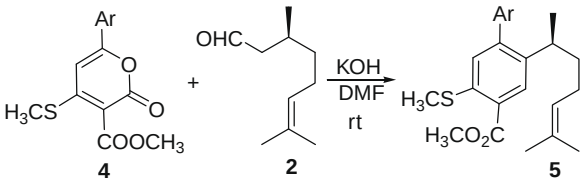
The chemistry of 2*H*-pyran-2-one derivatives is very interesting, which finds diverse synthetic applications as a diene component in Diels–Alder reactions.[16] During our recent studies on 2*H*-pyran-2-ones, we developed new methodologies for the synthesis of arenes,[17] pyridines,[18] pyridones[19] and polyarylbenzenes[20] through nucleophile-induced ring transformation reactions. The unique feature of 2*H*-pyran-2-ones **1** is the presence of three electrophilic centres: C2, C4 and C6, in which the latter is highly susceptible to nucleophilic attack due to the extended conjugation and the presence of the electron-withdrawing substituent at position 3 of the pyranone ring. The precursors 2*H*-pyran-2-ones **1** were conveniently prepared in high yields by the reaction of methyl 2-cyano-3,3-dimethylsulfanylacrylate with substituted acetophenones under alkaline conditions, followed by reaction with secondary amines.[17]

The synthesis of terpenylarenes **3a–f** was achieved by stirring a mixture of corresponding 2*H*-pyran-2-ones **1**, *S*-citronellal **2** and powdered KOH in DMF for 4–6 h at room temperature (Scheme 1). After usual work-up,[21] the crude product obtained was purified on silica gel column using 0.1% EtOAc in hexane as eluent.

A plausible mechanism for the formation of **3** involves Michael addition of conjugate base of *S*-(−)-citronellal at position C6 of lactone **1**, followed by intramolecular cyclization involving the carbonyl functionality of **2** and C3 of the pyranone ring, and then elimination of carbon dioxide, followed by dehydration.

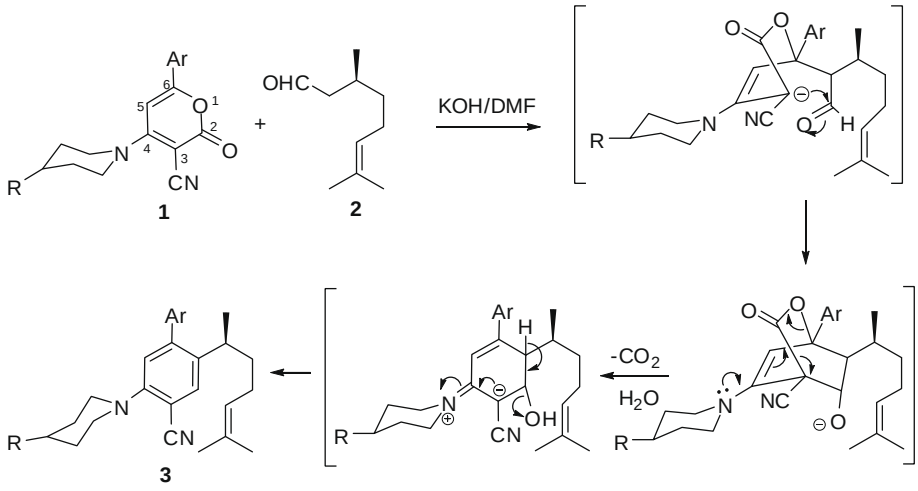
To demonstrate the utility of such an approach with functional group diversity, we undertook the synthesis of terpenylarenes **5a–f** with common electron-withdrawing and electron-donating groups. The successful reaction was carried out by stirring a mixture of 6-aryl-3-methoxycarbonyl-4-methylsulfanyl-2*H*-pyran-2-ones[17] **4**, *S*-(−)-citronellal and powdered KOH in DMF at ambient temperature (Scheme 2). Usual work-up and purification yield (*S*)-methyl 2-(6-methylhept-5-en-2-yl)-5-(methylsulfanyl)-biaryl-4-carboxylates **5a–f** in a single step from easily accessible precursors. The transformations of 6-aryl-2*H*-pyran-2-ones **4** into **5** possibly follow the pathway that is same as that described in Scheme 1.



5	Ar	Yield (%)
a	C_6H_5	57
b	4-ClC_6H_4	61
c	4-BrC_6H_4	59
d	4-$CH_3C_6H_4$	57
e	4-$CH_3OC_6H_4$	62
f	3,4-$(CH_2O_2)C_6H_3$	50

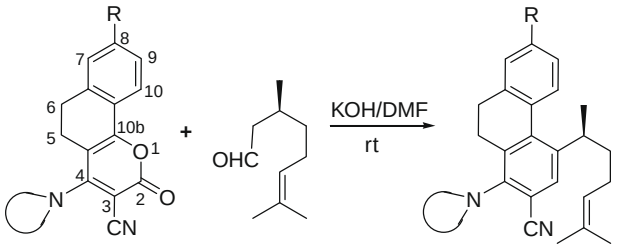
Scheme 2. Synthesis of terpenylarenes **5a–f**.

To further expand the scope of this reaction, interest is currently focused on synthesizing (*S*)-4-(6-methylhept-5-en-2-yl)-1-*sec*-amino-9,10-dihydrophenanthrene-2-carbonitrile **7** through ring transformation of 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitriles using *S*-(−)-citronellal as a source of carbanion. The easily accessible precursors 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitriles **6** used in the synthesis were prepared in two steps. The first step was the synthesis of 5,6-dihydro-4-methylsulfanyl-2-oxo-2*H*-benzo[*h*]chromene-3-carbonitriles via the base-catalyzed reaction of methyl 2-cyano-3,3-dimethylthioacrylate and 1-tetralone in DMSO. The reaction mixture was poured onto crushed ice with vigorous stirring to yield desired product, which on amination with a



3	Ar	R	Yield (%)
a	C_6H_5	H	58
b	4-BrC_6H_4	CH_3	69
c	4-$CH_3C_6H_4$	H	64
d	2-thienyl	CH_3	66
e	4-$CH_3OC_6H_4$	H	62
f	1-naphthyl	CH_3	50

Scheme 1. Probable mechanism involved in the synthesis of **3a–f**.



7	N—	R	Yields (%)
a	piperidin-1-yl	H	60
b	4-methylpiperidin-1-yl	H	61
c	4-benzylpiperidin-1-yl	H	62
d	4-benzylpiperazin-1-yl	H	51
e	morpholin-4-yl	H	63
f	tetrahydroisoquinolin-2-yl	H	65
g	piperidin-1-yl	OCH_3	54
h	4-methylpiperidin-1-yl	OCH_3	55

Scheme 3. Synthesis of terpenylarenes **7a–h**.

secondary amine in boiling ethanol afforded 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitriles[22] **6** (Scheme 3).

The topographical feature of the 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitriles **6** is similar to that of 2*H*-pyran-2-ones **1,** which has three electrophilic centres C2, C4 and C10b in which the latter is highly electrophilic and is prone to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing substituent at position 3 of the lactone ring. The conjugate base in this reaction is generated in situ from *S*-citronellal under alkaline conditions. Thus, a mixture of benzo[*h*]chromene **6**, *S*-(−)-citronellal **2** and powdered KOH in DMF was stirred for 2–3 h. The progress of the reaction was monitored by TLC, and on completion, the reaction mixture was poured onto crushed ice with vigorous stirring and was then neutralized with 10% HCl. The precipitate obtained was filtered, washed with water and dried. The crude product **7** was purified by neutral alumina column chromatography using 0.2% EtOAc in hexane as the eluent.[23]

In summary, we have demonstrated highly convenient and functional group tolerable one-step ring transformation approach for the synthesis of several sesquiterpene-cored aromatic compounds of synthetic and biological importance. This stereoselective protocol offers easy access to various terpenylarenes with the flexibility of introducing the electron-donor or electron-acceptor substituents that are essentially required in drug development perspectives.

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21. *General procedure for the synthesis of* **3a–f** *and* **5a–f**: A mixture of 6-aryl-2*H*-pyran-2-ones (**1a–f** and **4a–f**) (1 mmol), (*S*)-(−)-citronellal (1.2 mmol) and powdered KOH (1.5 mmol) in DMF was stirred at room temperature for 4–6 h. After completion of the reaction, excess DMF was removed under reduced pressure and was poured onto crushed ice with vigorous stirring. The solution was neutralized with 10% HCl, and the resulting precipitate was filtered, washed with water, dried and purified through silica column chromatography using 0.1% ethyl acetate in hexane as the eluent. (**3a**): Viscous oil; $[\alpha]_D^{25}$ +40.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.11 (d, *J* = 6.84 Hz, 3H, CH_3), 1.43–1.60 (m, 10H, $2CH_2$ and $2CH_3$), 1.69–1.80 (m, 6H, $3CH_2$), 2.71–2.83 (m, 1H, CH), 3.14 (t, *J* = 5.34 Hz, 4H, $2CH_2$), 4.83–4.88 (m, 1H, CH), 6.78 (s, 1H, ArH), 7.19–7.23 (m, 2H, ArH), 7.35–7.44 (m, 3H, ArH), 7.48 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.28, 21.08, 22.81, 24.31, 24.61, 24.88, 32.13, 37.01, 51.94, 103.98, 117.68, 118.82, 122.77, 126.13, 126.86, 127.55, 130.30, 130.63, 137.34, 139.58, 145.97, 152.60; IR (Neat) 2220 cm^{-1} (CN); MS (ESI) *m/z* 373 (M^++1); HRMS (EI) *m/z* calcd for $C_{26}H_{32}N_2$ 372.2566 found: 372.2595. (**5b**): Viscous oil; $[\alpha]_D^{25}$ +20.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, *J* = 6.87 Hz, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.48–1.63 (m, 5H, CH_2 and CH_3), 1.68–1.79 (m, 2H, CH_2), 2.40 (s, 3H, SCH_3), 2.71–2.80 (m, 1H, CH), 3.94 (s, 3H, OCH_3), 4.85–4.90 (m, 1H, CH), 6.99 (s, 1H, ArH), 7.17–7.21 (m, 2H, ArH), 7.38–7.42 (m, 2H, ArH) 7.95 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.33, 16.29, 21.09, 24.31, 24.65, 32.37, 36.92, 50.77, 122.75, 124.40, 125.25, 127.09, 127.93, 129.08, 130.40, 132.26, 138.00, 138.27, 139.64, 143.62, 165.54; IR (Neat) 1716 cm^{-1} (CO); MS (ESI) *m/z* 403 (M^++1); HRMS (ESI) calcd for $C_{23}H_{28}ClO_2S$: 403.14985, found: 403.15051.
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23. *General procedure for the synthesis of* **7a–h**: A mixture of 5,6-dihydro-2-oxo-4-*sec*.amino-2*H*-benzo[*h*]chromene-3-carbonitriles **6** (1 mmol) and S-(−)-

citronellal **2** (1.2 mmol) in dry DMF using KOH as base (1.5 mmol) was stirred for 2–3 h. After completion, excess of DMF was removed under reduced pressure and the reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% HCl. The crude thus obtained was purified by neutral alumina column chromatography using 0.2% EtOAc in hexane as the eluent. (**7a**) Viscous oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (d, J = 6.78 Hz, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.58–1.78 (m, 10H, $5CH_2$), 2.58–2.73 (m, 3H, CH and CH_2), 2.90–2.97 (m, 1H, CH), 3.15–3.20 (m, 4H, $2CH_2$), 3.37–3.45 (m, 1H, CH), 4.90 (t, J = 6.64 Hz, 1H, CH), 7.24–7.32 (m, 3H, ArH), 7.35–7.40 (m, 1H, ArH), 7.44 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.24, 21.29, 22.91, 24.18, 24.30, 24.51, 25.55, 28.32, 28.41, 32.55, 38.12, 51.20, 104.95, 118.68, 122.61, 124.51, 125.98, 126.43, 127.20, 130.15, 130.45, 132.55, 136.32, 138.96, 139.31, 148.87; IR (Neat) 2220 cm^{-1} (CN); MS (ESI) m/z 399 (M^++1); HRMS (EI) calcd for $C_{28}H_{34}N_2$: 398.2722, found: 398.2715.