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Iodine, a Mild Reagent for the Aromatization of Terpenoids

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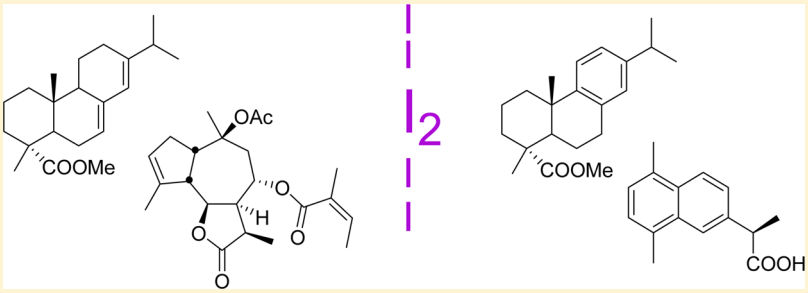
Supporting Information



ABSTRACT: Efficient procedures based on the use of iodine for the aromatization of a series of terpenoids possessing diene and homoallylic or allylic alcohol functionalities are described. Different examples are reported as a proof-of-concept study. Furthermore, iodine also proved to mediate the dehydrogenation of testosterone.

Aromatics are "privileged structures" widely distributed in different fields, such as the pharmaceutical industry and electronic materials.[1] A number of aromatic terpenes possessing interesting biological properties were reported (Figure 1).

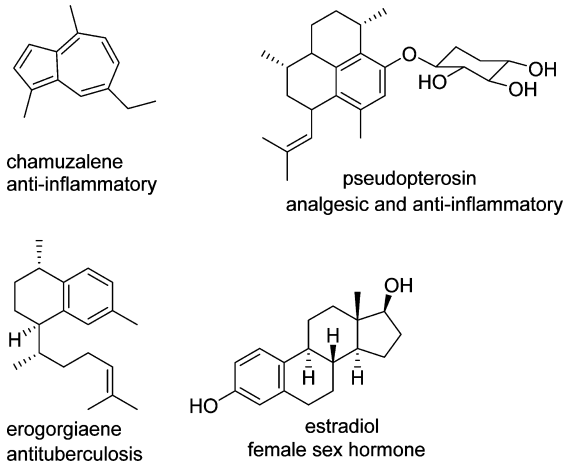


Figure 1. Examples of bioactive aromatic terpenoids.

Although the range of tools for aromatization is extremely wide, typical procedures require the use of metals and metal salts such as Pd black, SeO_2, $CuBr_2$–LiBr, MnO_2, $KMnO_4$, $CuCl_2$, $Cu(OAc)_2$, $FeCl_3$, and $Pd(OAc)_2$ among others.[2] Favored by the rapid emergence of Green Chemistry, metal-free strategies such as those published by Shi and others[3] are being reported to achieve different aromatizations. In this regard, iodine proved to play a key role in the development of modern synthetic methodologies, including some aromatization processes.[4]

To date, only a few examples have been reported on terpenoid aromatization by molecular iodine. Thus, some *p*-menthanes were reported to yield *p*-cymene by heating with iodine to 170 °C.[5] The sesquiterpenoid methyl nidorellaurinate was synthesized from a C_{12} triene intermediate after isomerization–aromatization mediated by iodine.[6] The diterpenoid isofregenedadiol was also prepared through a labdane intermediate by aromatization with iodine,[7] and the triterpenoid isokarounidiol was demethylated-aromatizated by heating in the presence of iodine.[8]

Noting that these iodine-mediated aromatizations were reported in isolation, we considered that new data helping to gain a comprehensive understanding of these aromatization deserved to be addressed, with the final goal being to widen the scope of this process, thus expediting the synthesis of aromatic terpenoids.

RESULTS AND DISCUSSION

Recently an iodine-mediated method for the synthesis of biphenyl starting from arylcyclohexenols (Scheme 1) was reported.[9] Assuming the intermediacy of the arylcyclohexadienes **I**, it was speculated whether a 4π system in a cyclohexane framework such as **III** would evolve to the corresponding aromatic analogues **II**. In this line of thinking,

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Scheme 1. Working Hypothesis

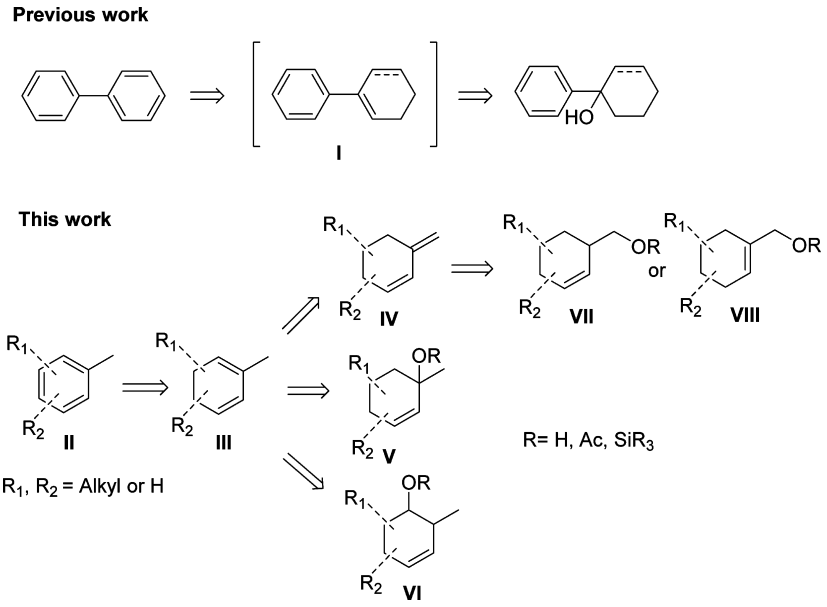

Table 1. Optimization of the Reaction Conditions

entry	starting material	solvent	I_2 (equiv)	time (h)	1	2	3	4	5a + 5b	aromatic compounds (%)
1	**1**	toluene	0.2[a]	4	51					
2	**1**	toluene	0.6	3	21	23	7	2	traces	32
3	**1**	benzene	0.6	8		37	20	15	3	72
4	**1**	benzene	1	6		40	26	22		86
5	**1**	**toluene**	**1**	**5**		**46**	**25**	**24**		**95**
6	**1**	xylene	1	0.7		28	43	29		89
7	**1**	MeCN	1	2.5	97					
8	**1**	MeOH	1	10	72				traces	
9	**1**	H_2O	1	12	68	9	3	1	traces	13
10	**1**	toluene	3	5		24	30	36		81
11	**1**	toluene	0.0015[b]	40	78	5	3		10	8
12	**1**	toluene	0.075[c]	3.5	76	3	10	5	2	13
13	**5a + 5b**	toluene	1	5		47	21	17		85

[a]5 equiv of DMSO was added. [b]Oxygen was bubbled through the reaction mixture. [c]5 equiv of TBHP was added.

the possible precursors of **III**, such as diene **IV** or allylic alcohols **V** and **VIII**, or even homoallylic alcohols **VI** and **VII**, may also well undergo this transformation.

The aromatization of terpenoids is complicated by the fact that most of the carbocyclic skeletons possess angular methyl groups. Consequently, the aromatization of these structures in many cases involves the migration of these tertiary methyl groups.[7,8] If the use of I_2 liberated significant quantities of HI, the presence of carbocationic intermediates could then be envisaged. The intermediacy of such cationic species would enable rearrangement and migration processes, thus permitting the aromatization of terpenes possessing quaternary carbons.

To study the feasibility of the approach, the sesquiterpenoid drimenol (**1**), a natural product available from *Drimys winteri*,[10] was used as starting material. The structure of **1** contains a homoallylic hydroxy group and an angular C-10 methyl group (type **VII** precursor, Scheme 1). For aromatization of the B-ring, elimination of the hydroxy group to give a diene with an exocyclic double bond, subsequent isomerization to an endocyclic diene, and a final methyl group rearrangement were required. Thus, when drimenol (**1**) was subjected to a mixture of I_2 (0.2 equiv) and DMSO (5 equiv) in toluene (optimized conditions recently published for the generation of biphenyls from arylcyclohexanols or arylcyclohexenols),[9] no aromatization products were produced, with only progressive degradation of the starting material being observed (Table 1, entry 1). The use of different solvents, variations of the quantity of iodine, and removal of DMSO (its ability to regenerate iodine from the HI resulting from the dehydrogenation processes is well-known)[9] were then addressed. When 0.6 molar equiv of I_2 was added to drimenol (**1**) in refluxing toluene or benzene, aromatic compounds **2**–**4** were produced (Table 1, entries 2, 3). The structures of these aromatic compounds were defined by spectroscopic (^{1}H, ^{13}C NMR, COSY, HSQC, HMBC, and 1D NOESY) and spectrometric analyses (HR-MS). Thus, the structure of compound **2** was assigned as the new pentasubstituted tetrahydronaphthalene derivative **2**, formed by the migration of Me-15 from C-10 to C-6. Compound **2** was accompanied by **3**, a nordrimane natural product with a tetrasubstituted tetrahydronaphthalene structure, produced by the loss of Me-15 and aromatization of the B-ring. This compound was isolated from *Isocoma wrightii*[11a] and synthesized from cyclohexene oxide in five steps by Barriault et al.[11b] as an intermediate in the synthesis of isofregenedol. The

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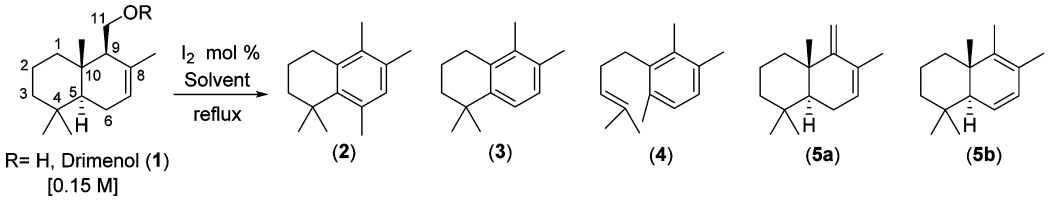
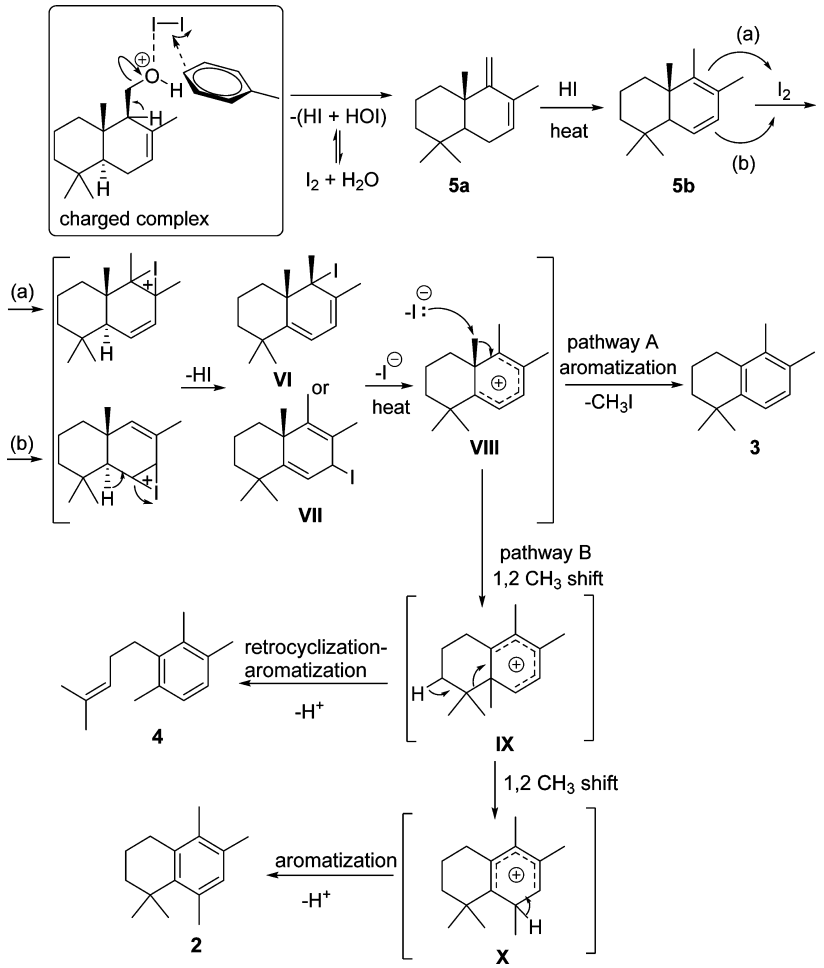
Scheme 2. Products Generated in the Iodine-Mediated Aromatization of Drimenol (1)



Scheme 3. Mechanism Proposed for the Iodine-Promoted Formation of 6−8



generation of compound **4** deserves to be emphasized since its formation includes a retrocyclization process in addition to the aromatization of the B-ring. Finally dienes **5a** and **5b** were produced as a result of dehydration of the starting alcohol **1**.

If the quantity of I_2 added to **1** was 1 equiv, the best aromatization result was obtained using toluene as a solvent with an excellent overall yield of 95% (Table 1, entry 5). In this case, compound **2** was formed in a 46% yield. Slightly worse results were obtained using benzene or xylene (Table 1, entries 4 and 6), although it should be noted that the use of xylene significantly shortened the reaction times.

Switching to polar solvents such as MeCN, MeOH, or H_2O (Table 1, entries 7−9) did not enhance the reaction outcome. In fact, aromatic compounds were generated with water as solvent in only 13% overall yield (Table 1, entry 9).

Finally, when the quantity of iodine was increased up to 3 equiv, the same three aromatic structures **2**−**4** were produced,[12] although in this case the *seco* derivative **4** represented the major reaction product (Table 1, entry 10).

With regard to the aromatization mechanism, the fact that only dienes **5a** and **5b** were detected with solvents such as MeOH, and when low quantities of reagent or shorter times were used, seems to indicate that the first step of the process is the coordination of iodine to the C-11 hydroxy function, thus causing its elimination to give **5a**. This would be transformed to **5b** via acid-catalyzed isomerization (Scheme 3). Subsequent reaction of these dienes with iodine would generate iododiene **VI** or **VII** via iodoiranium species. Iodide elimination would then lead to stabilized carbocationic intermediates **VIII**, **IX**, and **X**, the precursors to **2**−**4** through methyl rearrangements, retrocyclization, and/or aromatization processes (Scheme 3).

The intermediacy of dienes **5a** and **5b** was strongly supported by the fact that these compounds, synthesized as depicted in Scheme 4, were found to give similar results to those observed for drimenol (**1**) when subjected to the

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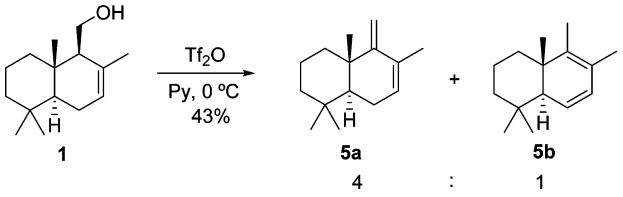
Scheme 4. Formation of Compounds 5a and 5b from 1



optimized aromatization conditions (Table 1, entry 13). According to the mechanistic proposal and with the final aim of rendering this process catalytic in iodine, the recycling of HI to molecular iodine was attempted via the usage of oxidants other than DMSO, e.g., O_2 or TBHP[13] (Table 1, entries 11, 12). However, no catalytic conditions were found, and the starting material was recovered as the main product after 12 h of reaction.

Once the work hypothesis was confirmed and the conditions for the iodine-mediated aromatization of drimenol (**1**) were established, these conditions were applied to the available terpenoid compounds decorated with diene systems or with homoallylic and allylic hydroxy groups in order to study the scope, advantages, and the limitations of the method (Table 2). The acetyl (**1a**) and silyl (**1b**) derivatives of the homoallylic alcohol **1** were found to be appropriate substrates for this transformation (Table 2, entries 1, 2). Efforts to aromatize the allylic alcohol (+)-clerodane acid (**6**)[14] (a type **VIII** diene precursor, Scheme 1) and the acetyl derivative **6a** led to the aromatization of the A-ring in acceptable yields (Table 1 entries 3, 4), with the compatibility of the free acid functionality worthy of note. The allylic alcohol 2-phenylcarveol (**8**) underwent aromatization in excellent yield to give the biphenyl derivative **9** (Table 1 entry 5).

To further explore the generality of the aromatization protocol, the homoallylic alcohol terpinen-4-ol (**10**) was subjected to the same reaction conditions; however, no acceptable quantities of *p*-cymene (**11**) were produced.[16] When the quantity of iodine was reduced, *p*-cymene (**11**) was detected in poor yield (Table 2, entry 6, a) and lower than that reported previously.[2d] This result prompted the use of other dehydrogenation conditions. Thus, after some experimentation with different reagents and conditions, it was determined that when terpinen-4-ol (**10**) was refluxed in toluene with a mixture of iodine (0.5 equiv) and the well-known oxidant DDQ[17] (0.5 equiv) for 45 min, a 78% yield of *p*-cymene (**11**) was obtained (Table 2, entry 6, b).

Continuing with the aim of gathering more data about the scope of the process, different types of dienes, either with both of the unsaturations belonging to the same ring or with one double bond located outside the ring to aromatize, were subjected to the aromatization conditions (Table 2, entries 7–9). The most satisfactory result was obtained from the aromatization of methyl hydroabietate (**13**) to methyl dehydroabietate (**14**) (Table 2, entry 8). It should be noted that diene **13** had previously been aromatized using Pd/C at 250 °C.[18] Therefore, the current method represents a considerable improvement if the simplicity of the experimental conditions are considered. When the diene limonene (**15**) was treated with 1 equiv of I_2, no acceptable quantities of *p*-cymene (**11**) were produced. However, the combined use of I_2 led to the formation of *p*-cymene (Table 2, entry 9) in good yield.

The last example in the terpene series was the aromatization of the guaiane carbon framework of compound **16**, isolated from *Seseli vayredanum* Font Quer,[20] to afford a 61% yield of the naphthyl derivative **17** (Table 2, entry 10). It is worth noting that **17** was generated as a consequence of an unusual cascade process that was proposed to start with an acetoxy elimination mediated by iodine, followed by a double Wagner–Meerwein rearrangement that caused a ring expansion and the generation of a rearranged eudesmane skeleton. The elimination of the side chain at C-8, followed by the lactone opening and aromatization, affords a scaffold similar to that of naproxen, a nonsteroidal anti-inflammatory drug[21] (Scheme 5).

These studies were completed by analyzing the iodine-promoted oxidation of steroids with an enone moiety located in the A-ring, where a 4π system can be envisaged through its enol form. However, the reaction of testosterone **18** with an equimolecular amount of iodine led to a rather complex mixture. Next, the behavior of testosterone when treated with iodine–DMSO was explored. Under these conditions, 6,7-dehydrogenation product **19** was produced, and the secondary hydroxy group remained intact (Scheme 6). It should be noted that Nicolaou recently reported the C-1–C-2 dehydrogenation of dihydrotestosterone using iodic acid in DMSO.[22] Besides compound **19**, minor quantities of the 3-iodo derivative **20** were also found, a derivative that was readily transformed into the 1,4,6-trienone **21** after 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) treatment. Compounds **19** and **21** represent metabolites of testosterone or of other prohibited substances in sports.[23] Although the aromatization of testosterone was not achieved, the dehydrogenation processes described for the formation of **19** and **21** constitute an environmentally friendly alternative to the conventional procedures reported for the synthesis of these compounds.[24]

In summary, an iodine-promoted method of aromatizing a number of different terpenoids is described. In some cases, the aromatizations also involve structural rearrangements. Allylic alcohols, free or as their *O*-acetyl or silyl derivatives, homoallylic alcohols, and dienes are susceptible to the aromatization process. Finally, iodine also proved to mediate the dehydrogenation of testosterone to afford either the corresponding 4,6-dienone or the 1,4,6-trienone, depending on the quantity of iodine employed.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured on a PerkinElmer 141 polarimeter. Silica gel SDS 60 (35–70 μm) was used for flash column chromatography. IR spectra were recorded on a Mattson Satellite FTIR spectrometer. NMR spectra were performed with Varian Direct-Drive 600 (^{1}H 600 MHz/^{13}C 150 MHz), Varian Direct-Drive 500 (^{1}H 500 MHz/^{13}C 125 MHz), Varian Direct-Drive 400 (^{1}H 400 MHz/^{13}C 100 MHz), and Varian Inova Unity 300 (^{1}H 300 MHz/^{13}C 75 MHz) spectrometers. Accurate mass determination was carried out with a mass spectrometer equipped with a TOF (Triwave Waters model SYNAP G2 system) and an AutoSpec-Q mass spectrometer arranged in an EBE geometry (Micromass Instruments, Manchester, UK) and equipped with a FAB (LSIMS) source. GC-MS analysis was performed on a Carlo Erba 8000 series model 8060, with a split ratio of 1:100 and 1 mL/min helium flow. The column temperature was held at 240 °C for 2 min, increased to 330 °C at a rate of 20 °C/min, and finally maintained at 330 °C for 15 min. A ZB-5 ms (30 m × 0.25 mm i.d., 0.25 μm film thickness, Phenomenex Inc., Torrance, CA, USA) column was used. The mass spectrometer ionization mode was electron impact (EI+), the acquisition mode was full scan (m/z range 45–500 Da), and the detector voltage was 70 eV. Reactions were monitored by TLC carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and solutions of phosphomolybdic acid in EtOH

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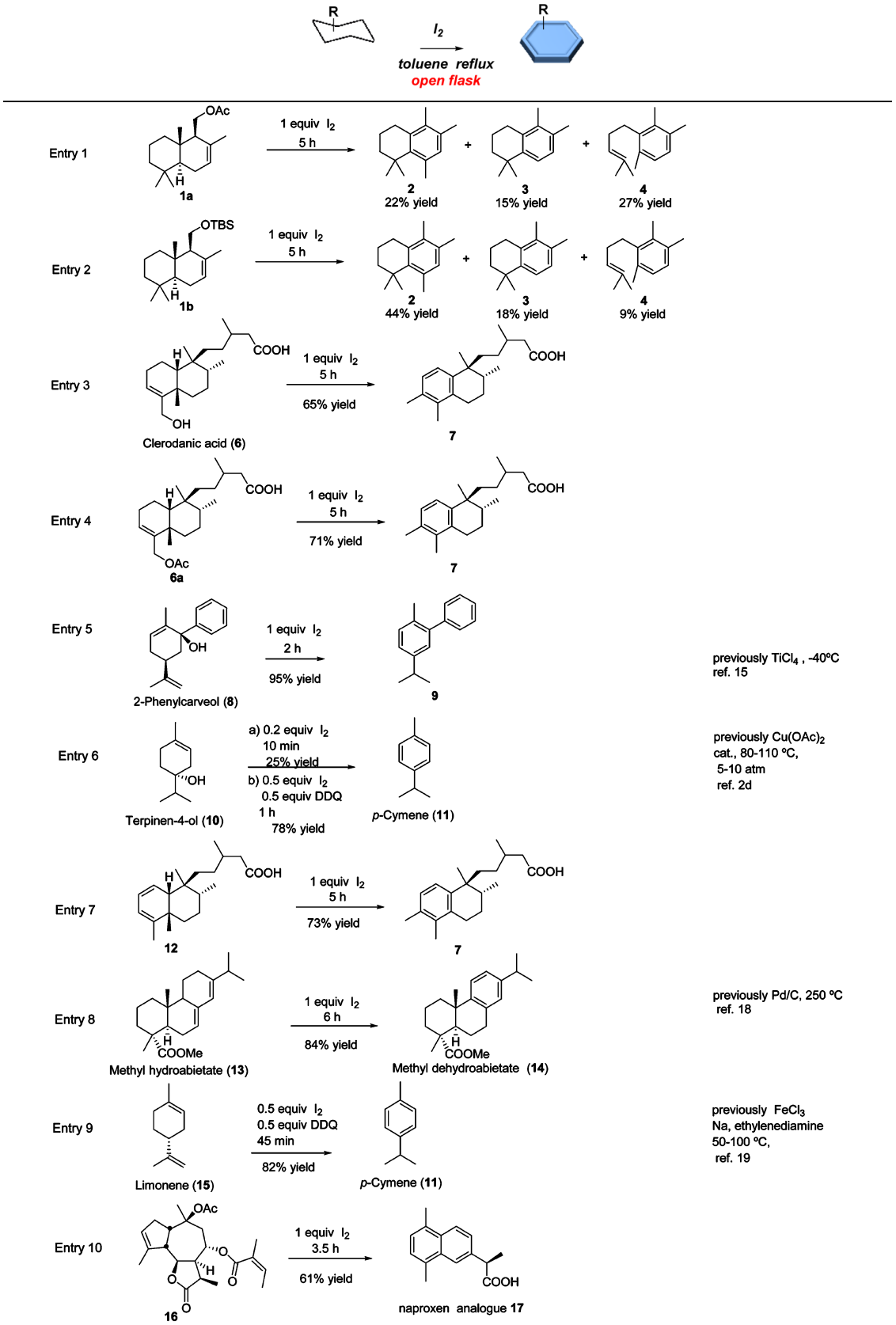
Table 2. Scope of Iodine-Promoted Aromatization



and heat as the developing agents. HPLC with UV and RI detection was used. Semipreparative HPLC separations were carried out on a column (5 μm silica, 10 × 250 mm) at a flow rate of 2.0 mL/min using an Agilent Series 1100 instrument. Reagents were purchased at the higher commercial quality and used without further purification.

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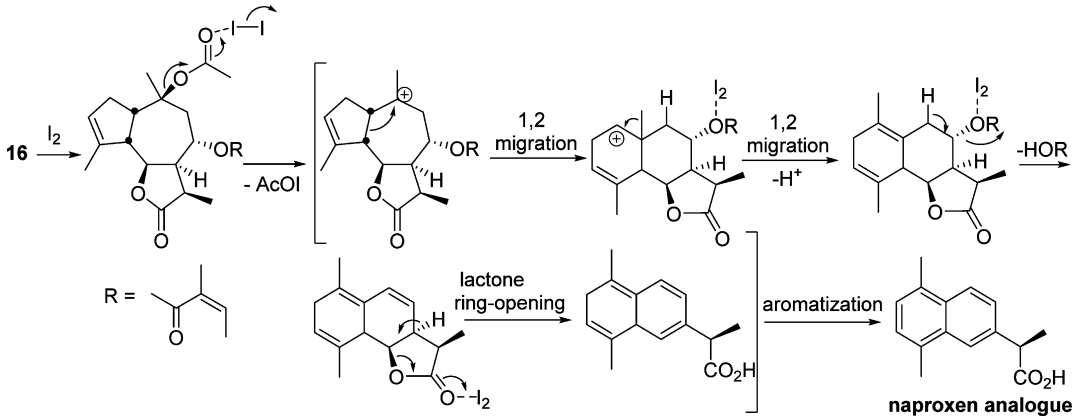
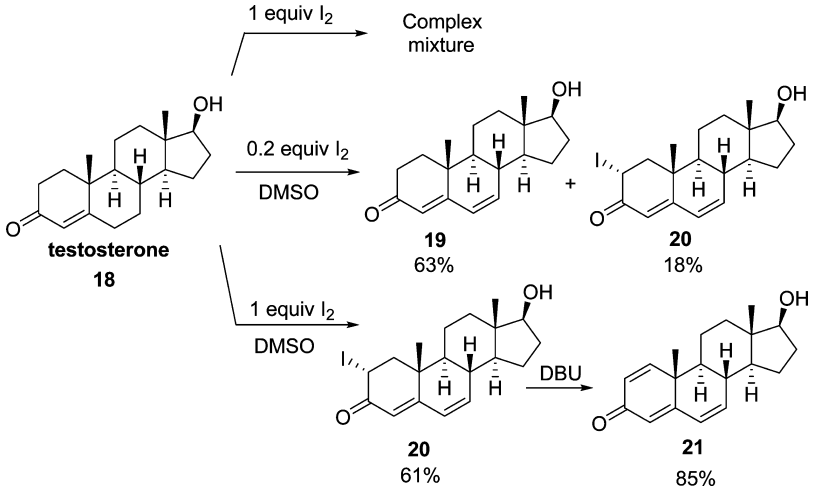
Scheme 5. Mechanistic Proposal for the Formation of Naproxen Analogue 17



Scheme 6. Iodine-Promoted Dehydrogenations of Testosterone



Aromatization Promoted by Iodine: Standard Procedure. To a solution of the corresponding allylic/homoallylic alcohol/diene (1 mmol, 1 equiv) in toluene (0.1−0.25 M) at reflux was added iodine (0.2−3.0 mmol). The solution was stirred at reflux and monitored by TLC analysis. If necessary, a second portion of iodine was added. Upon consumption of the starting material, the reaction was diluted in hexanes (100 mL) and washed with a saturated solution of sodium thiosulfate (1 × 100 mL), $NaHCO_3$ (1 × 100 mL), and brine (1 × 100 mL). The layers were separated, the aqueous layer was extracted with hexanes (2 × 50 mL), and the process was repeated. The organic layers were combined and dried over Na_2SO_4 and evaporated *in vacuo*. Purification was performed by silica gel chromatography to yield chromatographically and spectroscopically pure products.

Aromatization of Drimenol (1). Following the standard procedure, drimenol (**1**) (444 mg, 2 mmol) was dissolved in toluene (14 mL) and refluxed for 5 h. The resulting crude was column chromatographed using 20% w/w silica gel/$AgNO_3$ and *n*-hexane as the eluent to yield 185 mg of **2**, 94 mg of **3**, and 96 mg of **4**.

*4,4,6,8,9-Pentamethyl-1,2,3,4-tetrahydronaphthalene (**2**):* colorless oil; IR (film) ν_{max} 3062, 2930, 2865, 1454, 1260, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.05 (1H, s), 2.63 (2H, t, J = 6,5 Hz), 2.28 (3H, s), 2.18 (3H s), 2.16 (3H, s), 1.83 (2H, m), 1.28 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0 (C), 134.6 (C), 133.6 (C), 132.2 (C), 132.1 (C), 125.6 (CH), 38.9 (CH_2), 33.8 (CH_2), 32.1 (CH_3) (2C), 28.6 (CH_2), 21.1 (CH_3), 19.9 (CH_2), 15.9 (CH_3), 15.7 (CH_3); HRMS m/z 203.1799 (calcd for $C_{15}H_{23}$ $[M + H]^+$, 203.1722).

*4,4,8,9-Tetramethyl-1,2,3,4-tetrahydronaphthalene (**3**):* colorless oil; IR (film) ν_{max} 3064, 3008, 2937, 2885, 1482, 1455, 1382, 1260, 1066, 1031, 813 cm^{-1}; ^1H NMR ($CDC1_3$, 500 MHz,) δ 7.22 (1H, d, J = 8.0 Hz), 7.07 (1H, d, J = 8.0 Hz), 2.73 (2H, t, J = 6.5 Hz), 2.35 (3H, s), 2.22 (3H, s), 1.95−1.90 (2H, m), 1.72−1.69 (2H, m), 1.37 (6H, s); ^{13}C NMR ($CDC1_3$, 125 MHz) δ 143.6 (C), 134.6 (C), 134.5 (C), 133.3 (C), 127.4 (CH), 123.9 (CH), 38.7 (CH_2), 33.9 (C), 32.1 (CH_3) (2C), 28.4 (CH_2), 20.5 (CH_3), 19.7 (CH_2), 15.3 (CH_3); HRMS m/z 188.1563 (calcd for $C_{14}H_{20}$, 188.1565).

*5-(2′,3′,6′-Trimethylphenyl)methylpent-2-ene (**4**):* colorless oil; IR (film) ν_{max} 3072, 3030, 2962, 2924, 2865, 1460, 1378, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.96 (2H s,), 5.31 (1 H, t, J = 7.2 Hz), 2.71 (2H, m), 2.36 (3H, s), 2.30 (3H, s), 2.28 (2H, s), 2.18 (2H, m), 1.77 (3H, s), 1.66 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 138.9 (C); 134.5 (C), 134.4 (C), 133.6 (C), 131.9 (C), 127.4 (CH), 127.3 (CH), 124.2, (CH), 30.3 (CH_2), 28.0 (CH_2), 25.7 (CH_3), 20.8 (CH_3), 20.0 (CH_3), 17.6 (CH_3), 15.4 (CH_3); HRMS m/z 202.1718 (calcd for $C_{15}H_{22}$, 202.1722).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b00914.

Full experimental data as well as characterization and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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