SUSTAINABLE SYNTHESIS OF THE NATURALLY HYPOLIPIDEMIC AGENT α-ASARONE

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GRAPHICAL ABSTRACT

Abstract A short and practical preparation of α-asarone was developed using the inexpensive methylisoeugenol as a starting material. The utilization of a sequence of tribromination, debromination, and copper-mediated aromatic substitution enabled the stereoselective formation of only the E-isomer of α-asarone in good yield.

Keywords α-Asarone; atherosclerosis; cardiovascular; sustainable

INTRODUCTION

Today, one of the major causes of heart disease or cardiovascular hearth disease (CHD) in developed countries is atherosclerosis and associated conditions. One of the main causes is associated with hyperlipidemia or high blood lipid concentration. Among the lipids causing this condition are fats and fatty acids, along with cholesterol, phospholipids, and triglycerides. CHD such as atherosclerosis results from the formation of plaque inside the arteries—leading to the hardening and narrowing of the arteries, limiting the flow of nutrients and oxygen to organs such as the heart.[1]

The search for lipid-lowering drugs that may prevent the development of atherosclerosis has been a very active area of research.[2] Although CHD is mainly associated with lifestyle it is also obtained as a result of biosynthesis of cholesterol in the liver, which is regulated by the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMGR).[3,4] Therefore, if the biosynthesis of cholesterol...
in the human body can be inhibited, the prevalence of CHD associated with hyperlipidemia could be reduced. Evidence suggests that the reduction of low density cholesterol (LDLC) lowers the incidence of mortality associated with CHD. Among the most effective drugs that reduce the LDLC concentration in plasma are those that inhibit the HMGR.[5] Among the drugs used in the treatment of hyperlipidemia are statins, which are either natural compounds derived from fungi or analogs of them.[6] These drugs represent combined sales of several billion dollars worldwide.[7]

Another natural compound that possesses hypolipidemic activity is α-asarone 1 (Fig. 1). This is the main active component found on the extract of Guatteria gaumeri Greenman (Annonaceae) bark, a medicinal plant that is used in Mexico for the treatment of cholelithiasis or gallstones and hypercholesterolemia.[8] Because of this and other properties, such as insecticidal, antimicrobial, and nematicidal, α-asarone has received widespread interest. Some derivatives and analogs of α-asarone have been studied to modify their structures in order to explore their structure–activity relationship (SAR).[9]

Several methods for the synthesis of α-asarone 1 have been reported,[10] but most of these suffer from problems associated with the use of not readily available materials, which are prepared via multistep synthesis or expensive starting materials. Two of the main methods to form the conjugated double bond are based in the employment of a Wittig reaction[10b] or the use of Grignard reagents followed by dehydration[10a,d]. The main problem with these routes are poor yields in the assembly of the skeleton and/or lack of stereoselectivity, generating mixtures of the desired E isomer along with substantial amounts of the undesired and toxic Z isomer, which are difficult to separate or require an extra step in the isomerization reaction.[11]

In recent years, the use of biomass-derived chemicals in the synthesis of complex and useful compounds has been associated with sustainability and green chemistry.[12] There are several organic compounds of biological origin that are obtained in substantial amounts and are used in the perfumery, flavor, or drug industries.[13] In the search for a shorter and more stereoselective route to α-asarone, we considered the use of the inexpensive and readily available methylisoeugenol 2, which is used in perfumery. As can be noticed from the structure of 2, it only requires the installation of a methoxy group ortho to the propenyl chain to reach α-asarone. In this article we present the results of the synthesis of α-asarone from methyl isoeugenol 2.

Initially, we considered functionalization of C-5 in 2 to install a functional group capable of being converted either to a phenol or a more preferable methoxy group (Scheme 1). A previously reported synthesis of α-asarone uses the
bromoderivative 4 which, through a copper-mediated substitution, installs the methoxy function with excellent yield.\cite{10a} Thus, we were confronted with the issue of how to selectively install a good leaving group in the required position without affecting the double bond on the chain. We reasoned that a selective halogenation of the aromatic ring would be difficult in the presence of the double bond. Therefore, we considered that by employing an excess of halogen, we could halogenate the double bond and the aromatic ring in one step, installing the halogen in the required position, assisted by the aromatic methoxy groups and the chain.\cite{14} The selective dehalogenation of the chain dibromoderivative 3 could generate the bromocompound 4, which could be converted to 1 by the reported procedure.\cite{10a}

RESULTS AND DISCUSSION

The reaction of methylisoeugenol, consisting of a mixture of cis/trans isomers (70/30 ratio by gas chromatography, GC), was reacted with 2.2 equivalents of bromine in chloroform to afford the corresponding tribromoderivative 3 in 95% yield. The resulting diastereomeric mixture was used without purification in the debromination step. Debromination was carried out simply by refluxing crude 3 during 2 h with 3 equivalents of sodium iodide in acetone to afford 4 in 80% yield. NMR spectra showed that 4 consisted of essentially pure E isomer, which did not require any further purification. The observed stereoselectivity of the dehalogenation reaction to afford only the E isomer is concordant with the selectivity to trans elimination for vic-dibromides.\cite{15} Reaction of 4 with excess sodium methoxide in dimethylformamide (DMF) catalyzed by copper(I) bromide according to the published procedure\cite{10a} yielded \(\alpha\)-asarone 1 as the only isomer in 82% yield after purification. The spectral data of the obtained product was identical with the published data.

CONCLUSION

In summary, a short three-step stereoselective route to the lipid lowering agent \(\alpha\)-asarone from inexpensive and biomass derived starting material is reported. This route is amenable to adaptation for large-scale preparation of this compound.
**EXPERIMENTAL**

$^1$H and $^{13}$C NMR spectra were recorded using a Varian 500 instrument, and the chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard (0.00). The mass spectra were recorded on a Jeol JMS-SX102A spectrometer in the electron-impact (EI) mode at 70 eV and 200 °C via direct inlet probe. Only the molecular and parent ions (m/z) are reported. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 2000 instrument. All solvents and reagents were used as received. Flash column chromatography was carried on silica gel (Natland). All reactions were performed under nitrogen or argon.

1-Bromo-2-(1,2-dibromopropyl)-4,5-dimethoxybenzene 3

Bromine (3.52 g, 22 mmol) dissolved in CHCl$_3$ (5 mL) was slowly added to a stirred solution of methylisoeugenol 2 (1.78 g, 10 mmol) dissolved in CHCl$_3$ (50 mL) over 10 min. After this, the reaction mixture was stirred at rt for 2 h. Then, water (50 mL) was added and the phases separated. The organic phase was successively washed with an aqueous solution of 10% Na$_2$SO$_3$ (20 mL) and 1 N Na$_2$CO$_3$ (2 × 20 mL). The organic phase was dried (Na$_2$SO$_4$) and concentrated under vacuum. The dibromide 3 was obtained as a brown syrup which, was used immediately in the next step without further purification. Crude yield: 3.96 g (95%). A sample was purified by column chromatography (hexanes/EtOAc 8/2). This consisted of a mixture of two isomers. Major isomer 3b:

$^1$H NMR (500 MHz, CDCl$_3$) δ: 7.00 (s, 1H, H-3b), 6.98 (s, 1H, H-6b), 5.56 (d, J = 10.1 Hz, 1H, H-10b), 4.61 (dq, J = 10.2, 6.5 Hz, 1H, H-2'b), 3.90 (s, 3H, OMe), 3.88 (s, 3H, OMe), 2.04 (d, J = 6.2 Hz, 3H, H-3'b). $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 149.77 (C4, C5), 148.92 (C4, C5), 131.35 (C1), 114.98 (C6), 113.23 (C2), 111.14 (C3), 57.41 (C10), 56.19 (OMe), 56.16 (OMe), 56.13 (OMe), 50.44 (C20), 25.42 (C30).

Minor isomer 3a: $^1$H NMR (500 MHz, CDCl$_3$) 7.18 (s, 1H, H-3a), 6.97 (s, 1H, H-6a), 5.60 (d, J = 6.0 Hz, 1H, H-1'a), 4.51–4.43 (m, 1H, H-2'a), 1.77 (d, J = 6.8 Hz, 3H, H-3'a). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 149.74 (C4, C5), 148.90 (C4, C5), 129.98 (C1), 114.09 (C6), 58.55 (C1'), 56.19 (OMe), 56.16 (OMe), 56.13 (OMe), 53.55 (C2'), 24.46 (C3').

HRMS (EI$^+$) calculated for C$_{11}$H$_{13}$O$_2$Br$_3$: 413.8466; found: 413.8477.

(E)-1-Bromo-4,5-dimethoxy-2-(prop-1-en-1-yl)benzene 4

Crude 3 (3.96 g, 9.49 mmol) was added to a solution of NaI (4.26 g, 28.47 mmol) in acetone (100 mL). The mixture was heated to reflux during 3 h. The reaction mixture was concentrated in vacuo and the residue was diluted with hexanes (50 mL). To this mixture, water (100 mL) was added and the phases were separated. The aqueous phase was extracted with hexanes (25 mL). The combined organic phases were washed with 10% Na$_2$SO$_3$ (2 × 50 mL) and dried (Na$_2$SO$_4$). Solvent removal in vacuo left a viscous residue, which solidified to a cream-colored mass. Yield 1.94 g (80%). TLC (9:1 hexane/EtOAc) showed a single spot. IR: (ATR) cm$^{-1}$ 3084, 3002, 2958, 2911, 2839, 1651, 1599, 1567, 1503, 1463, 1437, 1384, 1339, 1256, 1195, 1162, 1029, 986, 959, 927, 854, 834. $^1$H NMR (500 MHz, CDCl$_3$): δ 6.97 (s, 1H, H-3'), 6.96 (s, 1H, H-6'), 6.64 (dq, J = 15.6, 85.6 Hz, 1H, H-2'), 5.60 (d, J = 10.6 Hz, 1H, H-1'a), 4.43 (dd, J = 10.6, 15.6 Hz, 1H, H-2'a), 1.77 (d, J = 6.8 Hz, 3H, H-3'a). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 149.74 (C4, C5), 148.90 (C4, C5), 129.98 (C1), 114.09 (C6), 58.55 (C1'), 56.19 (OMe), 56.16 (OMe), 56.13 (OMe), 53.55 (C2'), 24.46 (C3').

HRMS (EI$^+$) calculated for C$_{11}$H$_{13}$O$_2$Br$_3$: 413.8466; found: 413.8477.
(E)-1,2,4-Trimethoxy-5-(prop-1-en-1-yl)benzene (α-Asarone) 1

NaOCH₃ was prepared dissolving Na (5 g, mmol) in CH₃OH (100 mL). After the sodium reacted, most of the methanol was removed in the rotavapor, leaving a syrup containing NaOCH₃ and CH₃OH. This was diluted with dry DMF (50 mL), and Cu₂Br₂ (1.14 g) was added. The mixture was stirred, and 3 (4.12 g, 16.02 mmol) was added. The reaction mixture was heated under reflux during 24 h. The resulting mixture was subjected to evaporation in vacuo to remove most of the DMF, and the residue diluted with CHCl₃ (70 mL). The mixture was diluted with water (100 mL) and the phases separated. The aqueous phase was extracted with 25 mL of CHCl₃, and the combined chloroformic extracts were washed with water (5 × 25 mL). The extract was dried (Na₂SO₄) and concentrated in vacuo to afford a dark syrup, which was purified by flash chromatography on silica, eluting with 9:1 hexane/ethyl acetate. Yield 2.73 g (82%), yellowish oil that solidified on standing. IR (ATR) (cm⁻¹): 2996, 2955, 2852, 2833, 1608, 1586, 1509, 1504, 1460, 1438, 1299, 1270, 1202, 1178, 1031, 968, 860, 817. ¹H NMR (500 MHz, CDCl₃) δ: 6.94 (s, 1H, H-3), 6.65 (dq, J = 15.8, 1.6 Hz, 1H, H-1'), 6.49 (s, 1H, H-6), 6.14–6.04 (m, 1H, H-2'), 3.87 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.80 (s, 3H, OMe), 1.88 (dd, J = 6.6, 1.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ: 150.53 (C4, C5), 148.63 (C4, C5), 143.25 (C1) 124.95 (C2), 124.13 (C6), 118.90 (C1'), 109.74 (C3), 97.86 (C2'), 56.55 (OMe), 56.37 (OMe), 55.97 (C1′-OMe), 18.64 (C3'). HRMS (EI⁺) calculated for C₁₁H₁₃O₂Br: 256.0099; found: 256.0091. The spectral data of 4 agreed with the reported values. ¹⁰[a]–¹⁰[c]

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SUPPORTING INFORMATION

Spectral data for all compounds including ¹H and ¹³C NMR spectra and HRMS for this article can be accessed on the publisher’s website.
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