The first total synthesis of (±)-annosqualine by means of oxidative enamide–phenol coupling: pronounced effect of phenoxide formation on the phenol oxidation mechanism

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Abstract—The first total synthesis of a spiro-isoquinoline alkaloid, (±)-annosqualine, was established by employing an enamide–phenol coupling of a 1-methylene-1,2,3,4-tetrahydroisoquinoline derivative with a hypervalent iodine reagent, where the formation of the phenoxide was recognized to be an essential step for the reaction of the phenolic hydroxyl group with the hypervalent iodine reagent leading to the formation of the desired product.

Keywords: Annosqualine; Spiro-isoquinoline alkaloid; Iodobenzene diacetate; Enamide–phenol coupling; Phenoxide formation.

Annosqualine 1, a novel isoquinoline alkaloid with an unprecedented skeleton bearing a spirocyclohexadienone function, was isolated from the stems of Annona squamosa in 2004 as a minor component, and was supposed to be a biogenetic precursor of protoberberine and oxoprotoberberine alkaloids.1 Although the structure of 1 was elucidated spectroscopically, its synthesis and biological activity have not been studied yet (Fig. 1).

Recently, we have developed a facile synthetic procedure for a proaporphine alkaloid, (±)-stepharine, where an oxidative enamide–phenol coupling of an isoquinoline derivative with a hypervalent iodine reagent, iodobenzene diacetate (PIDA) in trifluoroethanol (TFE) leading to the formation of a spirocyclohexadienone moiety, was involved as the key step2 (Fig. 2).

In relation to a project directed at the synthesis of biologically active natural products by employing aromatic oxidation with a hypervalent iodine reagent,3–5 we are interested in establishing a concise synthesis of the unique isoquinoline alkaloid, annosqualine 1. Prior to the synthesis of the natural product, we decided to investigate efficient and mild reaction conditions for the oxidation of a readily available enamide 5 as follows (Scheme 1).

Condensation of the known 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride 3 with 4-(tert-butyldimethylsilyloxy)benzoyl chloride 2, prepared from 4-(tert-butyldimethylsilyloxy)benzoic acid,6 afforded enamide 4. Since an attempted isolation of the phenolic enamide 5, derived from 4 by desilylation with

Figure 1. Structure of annosqualine 1.

Figure 2. Our previous synthesis of proaporphine alkaloid.
tetrabutylammonium fluoride (TBAF) in tetrahydrofu-
rann, resulted in the easy formation of the hydrolysis
product 9, the crude enamide 5, obtained from the
above reaction mixture by evaporation of the solvent,
was subjected to oxidation without further purification.

First, we investigated the oxidation of 5 with the use of
PIDA as the oxidant, in TFE at room temperature, and
subsequent reduction of the presumed intermediate 6
with sodium borohydride in a one-pot procedure
according to our previous procedure;2 however, none
of the desired product 8 could be isolated under these
reaction conditions producing only decomposed prod-
ucts. However, we were pleased to be able to isolate ena-
mide 7 by careful examination of the reaction mixture
when this oxidation was conducted under the same reac-
tion conditions, without further treatment of an inter-
mediate with sodium borohydride, although the yield
was lower than 10%. Encouraged by this result, we next
focused our attention on searching for optimal condi-
tions for the oxidation, in which we decided to isolate spiro-enamide 7 instead of its one-pot conversion to 8
by subsequent reduction.

It is well recognized that the use of a solvent with less
nucleophilicity gives better result in an oxidative pheno-
lc coupling. Thus, a similar oxidation of 5 with PIDA
was carried out in hexafluoroisopropanol (HFIP) as
the solvent,7 instead of TFE; however, the desired
spiro-enamide 7 was again obtained in a trace amount.
At this point, we had to figure out the reason why the
oxidation of 5 did not proceed smoothly to give the
desired product, compared to our previous work,2 where
the oxidation gave the desired product in 90% yield. As
for this reason, we thought that there are two reactive
sites against the oxidant (PIDA), in the starting com-
 pound 5, a phenolic oxygen and an enamide carbon,
which might make the oxidation troublesome. Although
two reactive sites were also present in the starting mate-
rial of our proaporphine synthesis, the enamide nitrogen
of the starting isoquinoline was protected with a trifluo-
roacetyl group, a strong electron-withdrawing group,
which might diminish the reactivity of the enamide car-
bon with the oxidant to afford the desired product in
high yield. To prove this hypothesis, we decided to
add a base to the starting enamide prior to its further
oxidation, since generation of the phenoxide by addition
of a base would be expected to increase its reactivity
against the oxidant. Thus, the starting enamide 5 was
treated with 1.0 equiv of n-butyllithium in HFIP at
0 °C,8 and the resulting mixture was reacted with
1.0 equiv of PIDA at room temperature to give the de-
sired spiro-enamide 7 in 38% yield. When this reaction
was carried out in the presence of 2.0 equiv of n-butyl-
lithium, the yield was improved to 78%. The results
obtained are summarized in Table 1.

It is noteworthy that the reaction temperature for the
preparation of the phenoxide would be required to be be-
low 4 °C due to the instability of the starting enamide.9
Moreover, HFIP was obviously better than TFE as the
solvent in this reaction. The necessity of 2 equiv of n-
butyllithium would be attributed to trapping of acetic
acid generated from the reagent during the reaction
process, in addition to the formation of the phenoxide
to increase its reactivity against the oxidant.

Scheme 1. Preparation of enamide 4 and its conversion to 7.
With the desired spiro-enamide 7 in hand, we focused our attention on its reduction with sodium borohydride to obtain the basic carbon framework of the natural product. Again, it should be noted that the reduction of 7 with sodium borohydride in methanol, acetic acid, or TFE gave a complex mixture of products, whereas the use of HFIP as the solvent gave the desired product 8 in 91% yield (Scheme 2). Based on consideration of the above results, we attempted a one-pot preparation of 8 from 5 again, as follows.

Treatment of 5, derived from 4 as above, with 2 equiv of n-butyllithium in HFIP at below 4 °C, followed by oxidation of the resulting phenoxide with PIDA afforded the intermediate, which, without isolation, was further treated with sodium borohydride to provide the spirocyclohexadienone 8 in 52% yield. Thus, we were able to establish a one-pot synthetic procedure for 8 in reasonable yield.

By establishing a synthetic route to the basic skeleton of the natural product, we started the synthesis of annosqualine as follows. Our synthesis was launched with the preparation of the known aldehyde 14 by an alternative route in improved yield (Scheme 3).

Bromination of monobenzylpyrogallol 10 with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) gave the bromide 11 together with its regioisomer 12, in a ratio of 8:1. The structure of 11 was unambiguously determined based on its NMR analysis including NOE experiment. After methylation of phenolic oxygen with dimethyl sulfate, the resulting bromide 13 was treated with n-butyllithium, subsequently with N-formylmorpholine to provide aldehyde 14 in 90% yield. Since we were able to achieve the synthesis of the desired aldehyde 14 in good overall yield, preparation of 1-methyl-3,4-dihydroisoquinoline derivative 20 was then investigated (Scheme 4).
Condensation of 14 with nitromethane in the usual manner afforded nitrostyrene 15, which on reduction with lithium aluminum hydride in refluxing THF furnished phenethylamine 16. Acetylation of 16 with acetyl chloride gave amide 17 in 67% yield from 14. Benzyl ether 17 was transformed to its allyl ether 19, by two steps including a catalytic hydrogenation and allylation of the resulting phenol derivative 18 with allyl bromide in the presence of potassium carbonate, on consideration of the feasibility for its removal at the later stage of the synthesis. Bischler–Napieralski cyclization of 19 with phosphoryl chloride in benzene gave the 3,4-dihydroisquinoline hydrochloride 20, which, on treatment with 4-(tert-butyldimethylsilyloxy)benzoyl chloride, provided enamide 21 in 56% yield from 19.

Enamide–phenol coupling of 21, the key step in this synthesis, was carried out as follows (Scheme 5).

Desilylation of 21 with tetrabutylammonium fluoride in THF afforded the phenolic compound, which, without isolation, was treated with 2 equiv of n-butyllithium in


Scheme 5. Synthesis of annosqualine 1.
hexafluorosopropanol (HFIP). To this mixture was added iodobenzene diacetate (PIDA) at below 4 °C for 10 min to give spiro-enamide 22 successfully, in 73% yield from 21. Sodium borohydride reduction of 22 in HFIP gave the reduction product 2315 in 60% yield, whereas the use of sodium cyanoborohydride as the reducing agent could improve the formation of 23 to 86% yield.

Finally, deprotection of the allyl group of 23 with a catalytic amount of bis(triphenylphosphine)palladium(II) gave the reduction product 24 in 98% yield from 10 min to give spiro-enamide/C176 added iodobenzene diacetate (PIDA) at below 4 °C. The spectroscopic data (1H and 13C NMR) of the synthesized compound were identical with those provided by Professor Wu and Yang.

In summary, we are able to demonstrate the versatility of enamide–phenol coupling by its application to the first total synthesis of a naturally occurring spiro-isosquoline alkaloid, annosqualine 1. The strategy developed here would be applicable to the synthesis of various types of alkaloids, and further extension of this strategy is under investigation in this laboratory.

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References and notes

8. Treatment of n-BuLi with HFIP probably generated lithium hexafluorosopropropoxide, which on further treatment with 5 gave the corresponding phenoxide. These processes should be carried out at below 4 °C, due to the instability of the phenoxide. When these processes were conducted at room temperature, the starting 3,4-dihydroisoquinoline 3 was recovered as the degradation product.
9. Selected data for 8: Mp 223–224 °C. FT-IR (film) vmax 1700, 1650, 1520, 1230, 1100 cm−1; 1H NMR (500 MHz, CDCl3) δ 2.27 (dd, 1H, J = 22.7, 9.3 Hz, 9-H), 2.76 (dd, 1H, J = 16.1, 2.6 Hz, 4-H), 2.81 (dd, 1H, J = 12.7, 6.5 Hz, 9β-H), 2.97 (dd, 1H, J = 16.1, 11.6, 6.1 Hz, 4-H), 3.16 (br dt, 1H, 3-H), 3.87 (s, 3H, OMe); 13C NMR (125 MHz, CDCl3) δ 86.7 (C, 6-C), 43.4 (CH2, 5-C), 60.7 (OMe), 60.8 (OMe); MS [EI+] m/z 170 (M+); HR-MS [EI+] calcd for C19H19NO4 (M+) 325.1323; found 325.1323.
10. Selected data for 8: Mp 223–224 °C. FT-IR (film) vmax 1700, 1650, 1520, 1230, 1100 cm−1; 1H NMR (500 MHz, CDCl3) δ 2.27 (dd, 1H, J = 22.7, 9.3 Hz, 9-H), 2.76 (dd, 1H, J = 16.1, 2.6 Hz, 4-H), 2.81 (dd, 1H, J = 12.7, 6.5 Hz, 9β-H), 2.97 (dd, 1H, J = 16.1, 11.6, 6.1 Hz, 4-H), 3.16 (br dt, 1H, 3-H), 3.87 (s, 3H, OMe); 13C NMR (125 MHz, CDCl3) δ 86.7 (C, 6-C), 43.4 (CH2, 5-C), 60.7 (OMe), 60.8 (OMe); MS [EI+] m/z 170 (M+); HR-MS [EI+] calcd for C19H19NO4 (M+) 325.1323; found 325.1323.
13. Bromination of 1-benzyloxy-2,3-dimethoxybenzene under the same reaction conditions as described in Scheme 1 gave bromine 11 and its regioisomer 12 in a ratio of ca. 1:1.
14. Formylation of 13 with n-BuLi and DMF gave the desired aldehyde in 40–60% yield, and the corresponding primary alcohol was isolated in 30–40% yield, although the mechanism for its formation still remains obscure.
15. Selected data for 23: Mp 171–172 °C; FT-IR (film) vmax 1700, 1660, 1520, 1230, 1100 cm−1; 1H NMR (270 MHz, CDCl3) δ 2.25 (dd, 1H, J = 12.6, 9.4 Hz), 2.66–2.72 (m, 1H), 2.77 (dd, 1H, J = 12.6, 6.4 Hz), 2.91–2.98 (m, 1H), 3.10 (dt, 1H, J = 11.7, 4.6 Hz), 3.89 (s, 3H), 3.90 (s, 3H), 4.30–4.37 (m, 1H), 4.57 (br d, 2H), 4.95 (br dd, 1H), 5.30 (br dd, 1H), 5.42 (br dd, 1H), 5.99–6.13 (m, 1H), 6.39 (m, 3H), 6.70 (dd, 1H, J = 10.2, 3.0 Hz), 6.97 (dd, 1H, J = 10.2, 3.0 Hz); 11C NMR (67.8 MHz, CDCl3) δ 22.2, 39.7, 39.7, 53.6, 53.5, 53.7, 60.7, 63.6, 69.8, 69.9, 82.0, 123.1, 130.4, 131.0, 131.7, 132.9, 141.7, 144.3, 147.9, 151.4, 151.7, 168.1, 185.2; MS [EI+] m/z 382 (M+); HR-MS [EI+] calcd for C19H19NO4 (M+) 382.1654; found 382.1672.
17. Selected data for the synthetic I: Mp 222–223 °C. FT-IR (film) $\nu_{\text{max}}$ 1700, 1680 cm$^{-1}$; $^1$H NMR (500 MHz, CD$_3$OD) δ 2.30 (dd, 1H, $J$ = 12.5, 9.3 Hz), 2.69 (dddd, 1H, $J$ = 16.2, 11.3, 6.2, 1.1 Hz), 2.82 (dd, 1H, $J$ = 12.8, 6.8 Hz), 2.90 (ddd, 1H, $J$ = 16.2, 4.3, 2.3 Hz), 3.15 (ddd, 1H, $J$ = 13.2, 11.3, 4.6 Hz), 3.81 (s, 3H), 3.83 (s, 3H), 4.17 (ddd, 1H, $J$ = 13.2, 6.2, 2.3 Hz), 4.61 (s, 1H), 5.06 (dd, 1H, $J$ = 9.3, 6.8 Hz), 6.38 (dd, 1H, $J$ = 10.0, 3.1 Hz), 6.39 (dd, 1H, $J$ = 10.0, 3.1 Hz), 6.47 (d, 1H, $J$ = 0.6 Hz), 6.87 (dd, 1H, $J$ = 10.0, 3.1 Hz), 7.22 (dd, 1H, $J$ = 10.0, 3.1 Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) δ 23.2, 39.3, 40.4, 55.0, 55.4, 60.9, 61.0, 108.6, 119.3, 130.5, 132.0, 133.5, 141.3, 147.7, 151.2, 151.3, 152.4, 170.2, 187.7; MS [EI+] $m/z$ 341 (M$^+$); HR-MS [EI+] calcd for C$_{19}$H$_{19}$NO$_5$ (M$^+$): 341.1263; found 341.1287.