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Application of intramolecular Dötz reaction to the synthesis of ansa-compounds: concise synthesis of arnebinol

Masahito Watanabe, Kyosuke Tanaka, Yoko Saikawa* and Masaya Nakata*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

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Abstract—Fischer carbene complexes having long alkynyloxy chains regioselectively produced oxametacyclophanes via the intramolecular Dötz reaction. The utility of this reaction was demonstrated in the synthesis of arnebinol, an ansa-type terpenoid, from geranyl acetate in six steps.

The complex chemical structures and the various biological activities of ansa-compounds (or ansamycins)[1] have attracted great attention in the organic synthetic community. The general synthetic approaches to these ansa-compounds involve elongation of an alkyl chain (an ansa-chain) from an aromatic core followed by macrocyclization at the appropriate position.[2] As a new synthetic approach to ansa-compounds, we focused on the Dötz reaction.[3,4] We anticipated that the ansa-compounds having oxametacyclophane skeletons, for example, kendomycin (**1**),[5] coleophomone A (**2**),[6] and arnebinol (**3**),[7] would be synthesized featuring the intramolecular Dötz reaction (Fig. 1; bold lines show oxametacyclophane skeletons).[8]

It has been ascertained that the regiochemistry of the intermolecular Dötz reaction using Fischer chromium–carbene complexes and unsymmetrical alkynes is controlled by unfavorable steric interactions between the large substituent (R^L) of the alkyne and the carbene ligand at the incorporation stage of the alkyne (Scheme 1).[4] Thus, the major isomer of the obtained *p*-alkoxyphenols has the vicinal R^L and hydroxy substituents. For the intramolecular version of this benzannulation reaction with three types of carbene complexes **4**–**6** bearing the tethered alkynes, the six kinds of products **7**–**12** are possible; among them, when C^* is sterically larger than R^3, compounds **7**, **9**, and **11** would be the major products based on the assumption that the selection rule

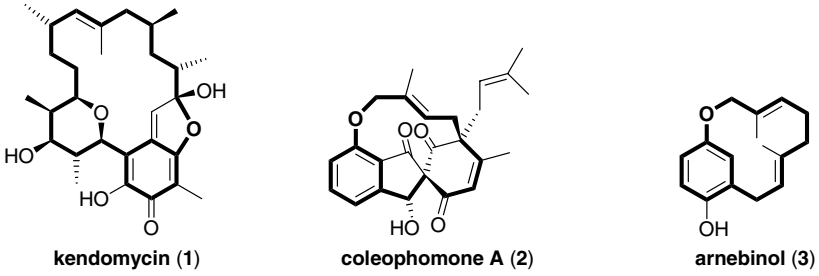

Figure 1. Examples of natural products having oxametacyclophane skeletons.

Keywords: Dötz reaction; Fischer carbene complex; Ansa-compound; Arnebinol.
* Corresponding authors. Tel.: +81 45 566 1562; fax: +81 45 566 1551 (Y.S.); tel.: +81 45 566 1577; fax: +81 45 566 1551 (M.N.); e-mail addresses: saikawa@applc.keio.ac.jp; msynktxa@applc.keio.ac.jp

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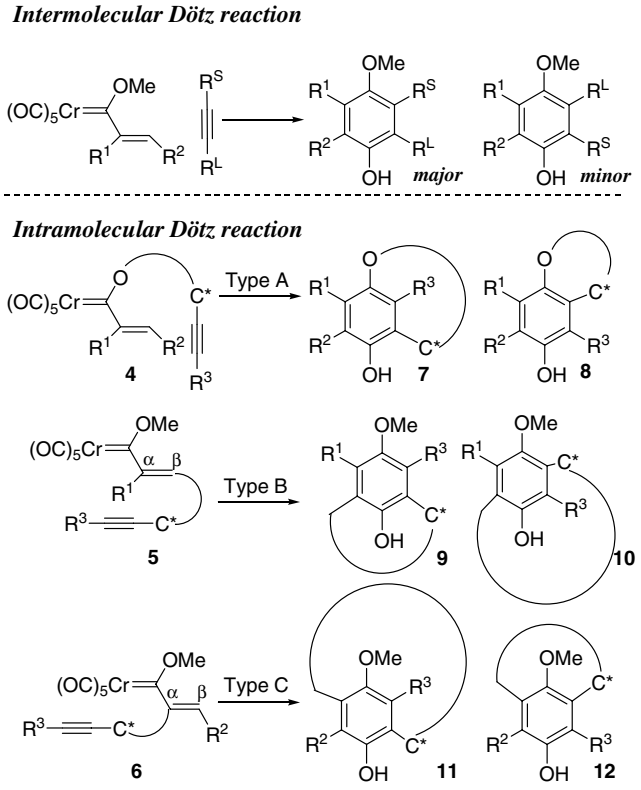
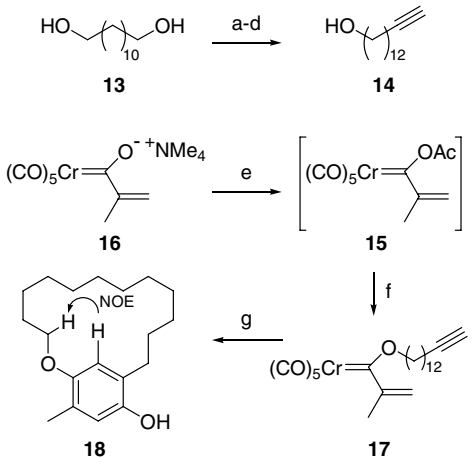


Scheme 1. Regiochemistry in inter- and intramolecular Dötz reactions with various chromium–carbene complexes.



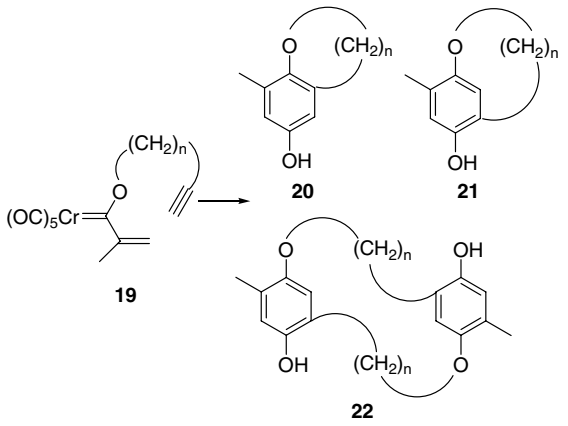
Scheme 2. Synthesis of the carbene complex **17** and its benzannulation. Reagents and conditions: (a) TrCl (1.0 mol amt), Et_3N (1.5 mol amt), DMAP (0.05 mol amt), CH_2Cl_2, rt, 1 h, 59%; (b) TsCl (1.0 mol amt), Et_3N (1.5 mol amt), DMAP (0.1 mol amt), CH_2Cl_2, rt, 3.5 h, 91%; (c) lithium acetylide ethylenediamine complex (2.0 mol amt), DMSO, rt, 2 h, 89%; (d) camphorsulfonic acid (0.1 mol amt), MeOH–CH_2Cl_2, rt, 2 h, quantitative yield; (e) AcBr (1.1 mol amt), CH_2Cl_2, −78 °C, 1.5 h; (f) **14** (1.0 mol amt), CH_2Cl_2, −78 °C, 3 h, 83%; (g) degassed solvents (0.002 M for **17**): 50 °C, 3 h, 29% (hexane): reflux, 3 h, 41% (Et_2O): 50 °C, 3 h, 50% (benzene): 50 °C, 3 h, 52% (toluene). Tr = triphenylmethyl, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, Ts = *p*-toluenesulfonyl.

in the intermolecular version is applicable. Compound **7** possesses the oxametacyclophane skeleton corresponding to the natural products **1**–**3**. Therefore, we expected that the type A reaction would realize the simultaneous benzannulation and cyclization of the ansa-chain to give the ansa-compound skeleton in one step. The reported examples of the type A, however, show that orthocyclophane **8** was obtained from **4** as the sole product due to the short tether.[9] In contrast, the β-tethered alkenyl complexes **5** (type B) preferably produced the expected metacyclophane **9**.[10] A reversal of the regiochemistry of the cyclization was achieved when $R^3 = Ph$ and $C^* = CH_2$ ($R^3 > C^*$), producing paracyclophane **10** as the major isomer.[10a] The α-tethered alkenyl complexes **6** (type C) showed a behavior similar to the type B cases, giving the expected paracyclophane **11** along with some unexpected rearranged products instead of **12**.[11] There have been no reports, to the best of our knowledge, about preparing metacyclophane **7** via the type A intramolecular Dötz reaction. It is anticipated that carbene complexes **4** with the long tether length would give oxametacyclophanes **7** corresponding to the desired ansa-compounds. We selected the chromium–carbene complex **17** (vide infra) as the model substrate to verify this hypothesis.

The synthesis of the designed carbene complex **17** started with dodecane-1,12-diol (**13**) by the four-step transformation into tetradec-13-yn-1-ol (**14**) (Scheme 2). Alkynyl alcohol **14** was introduced to acetoxyvinylidenechromium carbene complex **15**,[12] prepared in situ by treatment of tetramethylammonium salt **16**[13] with acetyl bromide, to give alkynyloxy carbene complex **17**. The resulting complex **17** was then subjected to the intramolecular Dötz reaction (50 °C, 3 h) in various solvents. In hexane, Et_2O (reflux), benzene, and toluene, the anticipated oxa-[13]-metacyclophane **18** was obtained as the major product in 29%, 41%, 50%, and 52% yields, respectively. The reaction in THF resulted in a complex mixture. The regiochemistry of **18** was confirmed by the NOE experiment and the absence of the coupling between the aromatic hydrogens in the ^1H NMR studies. From the viewpoint of the yield and reproducibility, we chose toluene as a suitable solvent for further investigations.

A more extensive study of the effect of the tether length was investigated and the results are shown in Table 1. Alkynyloxy carbene complexes **19a**–**h** were prepared by the same method as described above from ammonium salt **16** with the corresponding alkynyl alcohols, which are either commercially available or easily prepared by the isomerization of their internal alkyne isomers.[14,15] Hexynyloxy carbene complex **19a** produced oxa-[5]-orthocyclophane **20a** and dioxa-[5,5]-metacyclophane **22a** in 22% and 8% yields, respectively (entry 1). Heptynyloxy carbene complex **19b** favored dimerization rather than orhtocyclization, leading to dioxa-[6,6]-metacyclophane **22b** in 28% yield (entry 2). With the middle chain ($n = 6$ and 7) complexes, **19c** and **19d**, the reaction resulted in a complex mixture, in which the major products were dioxa-[n+1,n+1]-metacyclophanes **22c** and **22d** (entries 3 and 4). As the alkynyloxy chain became longer (**19e**–**h** and **17**), the yields of oxa-[n+1]-metacyclophanes **21e**–**h** (and **18**) increased and

Table 1. Intramolecular Dötz reaction of carbene complexes **19a–h**[a]



Entry	Substrate	Yield[b] (%)		
		20	**21**	**22**
1	**19a** ($n = 4$)	22	0	8
2	**19b** ($n = 5$)	8	0	28
3	**19c** ($n = 6$)	5	—[c]	34
4	**19d** ($n = 7$)	—[c]	4	21
5	**19e** ($n = 8$)	0	13	15
6	**19f** ($n = 9$)	0	19	7
7	**19g** ($n = 10$)	0	29	6
8	**17** ($n = 12$)	0	52 (=**18**)	0
9	**19h** ($n = 15$)	0	54	0

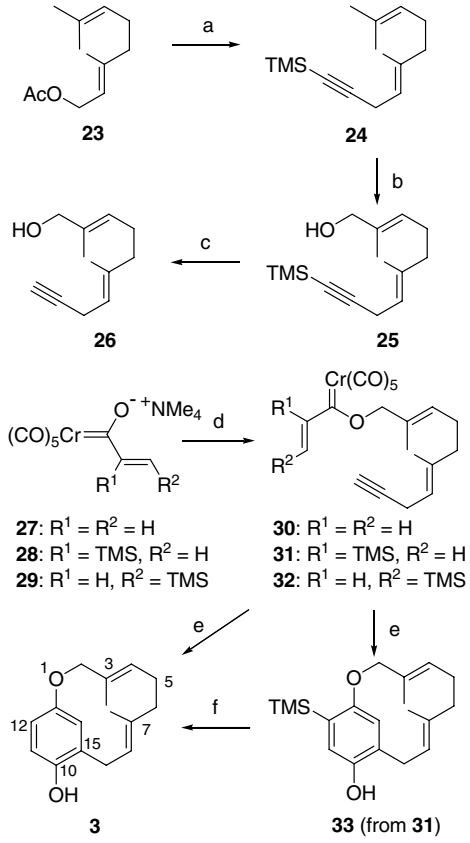
[a] All reactions were run at 0.002 M in toluene at 50 °C for 4 h under an argon atmosphere.

[b] Isolated yield after silica-gel column chromatography. All reaction mixtures contain some kinds of as-yet unidentified by-products.

[c] Not found.

those of the dimers **22e–h** decreased (entries 5–9). Apparently, these results suggest that the intramolecular Dötz reaction of **4** (type A) having a sufficient length of the alkynyloxy chain tends to metacyclize to give oxa-[n+1]-metacyclophane **7** in line with the intermolecular preference.

Encouraged by these results, we applied the intramolecular Dötz reaction to the synthesis of the ansa-type monoterpenylbenzenoid arnebinol (**3**). Arnebinol (**3**) was isolated from *Arnebia euchroma* in 1983[7] and synthesized by Mori's group from geranyl acetate in 1984.[16] Alkynyl alcohol **26** was prepared from geranyl acetate (**23**) in three steps as follows (Scheme 3). Geranyl acetate (**23**) was substituted with TMS acetylide in the presence of (DPEphos)$PdCl_2$ according to Negishi's method[17] to give dienyne **24** in 62% yield. Allylic oxidation of **24** with SeO_2[18] afforded **25** in 37% yield. Removal of the TMS group was realized using aqueous KF[19] without isomerization of the alkyne to the allene, affording the desired alkynyl alcohol **26** in 98% yield. This was incorporated into the three types of carbene complexes **27–29**[20,21] to afford **30–32**, respectively. Among them, both **30** and **32** were not very stable, therefore the isolated yields were low (30% and 26%, respectively); in contrast, **31** was obtained in 82% yield due to its good stability. The benzannulation of **30–32** in toluene at 60 °C showed a different behavior. The unstable **30** produced a fairly good yield of arnebinol (**3**) (49%); the stable **31** gave **33** (32%) together with a



Scheme 3. Synthesis of arnebinol (**3**). Reagents and conditions: (a) trimethylsilylacetylene (1.2 mol amt), *n*-BuLi (1.1 mol amt)/hexane, THF, −78 °C, 0.5 h, then $ZnBr_2$ (1.1 mol amt), −78 °C to 0 °C, 25 min, then (DPEphos)$PdCl_2$ (0.005 mol amt), **23** (1.0 mol amt)/DMF, 70 °C, 1.5 h, 62%; (b) SeO_2 (0.1 mol amt), TBHP (17 mol amt)/CH_2Cl_2, salicylic acid (0.1 mol amt), CH_2Cl_2, rt, 6 h, 37%; (c) KF (5.5 mol amt), H_2O (4.5 mol amt), DMF, rt, 16 h, 98%; (d) **27**, AcBr (1.1 mol amt), CH_2Cl_2, −78 °C, 0.5 h, then **26**, −78 to 0 °C, 30% (for **30**): **28**, AcBr (1.1 mol amt), CH_2Cl_2, −78 °C, 1 h, then **26**, 0 °C to rt, 82% (for **31**): **29**, AcBr (1.2 mol amt), CH_2Cl_2, −78 °C, 1.5 h, then **26**, −78 to −10 °C, 1 h, 26% (for **32**); (e) toluene (degassed, 0.002 M), 60 °C, 6 h, 49% (from **30**): 60 °C, 3 h, 32% (from **31** to **33**): 60 °C, 3 h, 21% (from **32**); (f) TFA (9.3 mol amt), CH_2Cl_2, 0 °C, 0.5 h, 83%. DPEphos = bis(2-diphenylphosphinophenyl)ether, TBHP = *tert*-butylhydroperoxide.

significant amount of the cyclic dimer (13%). The resulting **33** was desilylated with TFA to give arnebinol (**3**) in 83% yield. The unstable **32** directly gave **3** accompanied by the silyl C → O migration and desilylation,[20] allbeit in a low yield (21%). No regioisomer (oxa-[9]-orthocyclophane) was observed in all the benzannulation products. From the viewpoint of sample-handling easiness and overall yield, the route of **28** → **31** → **33** → **3** was adopted. The analytical and spectroscopic data of the synthetic sample of arnebinol (**3**) matched those of the natural product[7] and Mori's results.[16,22]

In summary, we described here the fundamental investigation of the type A intramolecular Dötz reaction and the application of this reaction to the regioselective synthesis of arnebinol (six steps). Syntheses of more functionalized ansa-compounds using this reaction are now in progress in our laboratories.

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22. The reported assignments[7] of ^{13}C NMR spectrum were partially revised. Arnebinol (**3**): a colorless prism; mp 163.5–165.8 °C (benzene) (lit.[7] 163.5–164 °C (benzene), lit.[16a] 159–160 °C (benzene), lit.[16b] 161.5–163.0 °C (benzene)); UV (EtOH) λ_{max} nm ($\log\varepsilon$): 214.5 (4.34), 292 (3.53) [lit.[7] 213.2 (4.42), 294.2 (3.83), lit.[16b] 203 (4.36)]; IR (KBr) ν_{max} cm^{-1}: 3423, 2941, 2905, 2840, 1507, 1458, 1440, 1420, 1342, 1253, 1192, 1145, 988, 850, 803; ^1H NMR ($CDCl_3$, $CHCl_3 = 7.26$): δ 1.25 (3H, s, 7-Me), 1.51 (3H, s, 3-Me), 2.14 (1H, br s, H-5), 2.34 (2H, t, $J = 7.0$ Hz, H-6), 2.49 (1H, br s, H-5), 3.07 (1H, br s, H-9), 3.30 (1H, br s, H-9), 4.32 (1H, s, OH), 4.54 (2H, br s, H-2), 5.53 (1H, br t, $J = 7.0$ Hz, H-4), 5.68 (1H, br t, $J = 7.0$ Hz, H-8), 6.56 (1H, dd, $J = 8.5$, 2.6 Hz, H-12), 6.60 (1H, d, $J = 8.5$ Hz, H-11), 7.45 (1H, d, $J = 2.6$ Hz, H-14); ^{13}C NMR ($CDCl_3$, $CDCl_3 = 77.00$): δ 12.64 (3-Me), 14.76 (7-Me), 25.28 (C5), 25.77 (C9), 39.24 (C6), 76.58 (C2), 115.03 (C11 or C12), 115.29 (C12 or C11), 118.13 (C14), 124.08 (C8), 127.08 (C15), 132.56 (C3), 133.64 (C4), 140.30 (C7), 146.84 (C10), 151.75 (C13); HR-EI-MS *m/z* calcd for $C_{16}H_{20}O_2$ ($[M]^+$) 244.1463, found 244.1460.