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Cyclohepta[de]naphthalenes and the Rearranged Abietane Framework of Microstegiol via Nicholas Reaction Chemistry

Rafiq A. Taj, Anusha Abhayawardhana, James R. Green*
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Abstract: Nicholas reactions on 2,7-dioxygenated naphthalenes give C-1 monosubstitution and C-1/C-8 disubstitution in most cases. From γ- carbonyl cation monocondensation product 3b or alkyne- unsubstituted dicondensation product 4a, cyclohepta[de]naphthalenes bearing no substituents, gem-dimethyl substituents, and a ketone function, and the rearranged abietane framework of microstegiol may be prepared.

Key words: Carbocations, alkyne complexes, transition metals, electrophilic aromatic substitution, ring closure, tautomerism.

We have a long standing interest in the synthesis of seven-membered ring systems, particularly involving the chemistry of alkyne dicobalt complexes and propargyldicobalt cations. In particular, we have developed chemistry to incorporate nucleophiles, including electron rich aranes, γ- to electron withdrawing groups, in an umpolung fashion, and have used this chemistry to get access to seven membered ring systems. In this context we were drawn to cyclohepta[de]naphthalenes, featured in the rearranged abietane framework of microstegiol or salvibretol. Compound 1 showed sufficient nucleophility to react with propargyldicobalt cations; propargyl alcohol complex 2a underwent BF\(_3\)-OEt\(_2\) mediated reaction to give 3a in excellent yield (93%) (Table 1). Use of γ- carbonyl cation precursor 2b (R\(_1\) = CO\(_2\)Me) gave good yields of condensation product 3b (76%), while substitution on the remote alkene carbon with methyl (2c) and trimethylsilyl (2d) functions also allowed formation of condensation products (3c-d) successfully (3c, 84%; 3d, 71%). Polyalkylation of the naphthalene nucleus did not appear to be a significant problem.

Table 1 Monocondensation reactions of 1

<table>
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<tr>
<th>Complex</th>
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<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>2a</td>
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<td>93</td>
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<tr>
<td>2b</td>
<td>CO(_2)Me(^a)</td>
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<td>76</td>
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<tr>
<td>2c</td>
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<tr>
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\(^a\) Compound 2b was employed as the methyl ether
\(^b\) Reaction conducted at 0 °C – RT.

Disubstitution reactions on 1 could also be accomplished, by increasing the amount of propargyldicobalt cation precursors (2) to 2.2 equiv. For these reactions, the predominant 1,8-disubstitution pattern (4) was observed only for the unsubstituted (R\(_1\) = H) and electron withdrawing group substituted (R\(_1\) = CO\(_2\)Me) propargyl cation complex precursors 2a and 2b (Table 2). In the case of other \(R_1\) substituents (R\(_1\) = Me, Me\(_3\)Si), the second substitution occurred at C-6, giving 5c and 5d. In the case of 2d (R\(_1\) = Me\(_3\)Si), the second condensation was somewhat sluggish, and substantial amounts of 3d were isolated in addition to 5d despite allowing the reaction to warm to room temperature.

Table 2 Dicondensation reactions of 1

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Microstegiol and oxomicrostegiol, X = H; Microstegiol, X = O

Salvibretol and oxosalvibretol, X = H; Salvibretol, X = O

Figure 1 Rearranged abietanes containing cyclohepta[de]naphthalene nucleus.

As a starting point to test reactivity, 2,7-dimethoxynaphthalene (1) was chosen, by virtue of its ready availability, its ability to direct monosubstitution to C-1 over C-3 in most cases and disubstitution to C-1/C-8 over C-1/C-6 in many cases, and the potential for one alkoxy to serve as the masked version of the ketone function in microstegiol or salvibretol. Compound 1,2 showed sufficient nucleophile to react with propargyldicobalt cations; propargyl alcohol complex 2a underwent BF\(_3\)-OEt\(_2\) mediated reaction to give 3a in excellent yield (93%) (Table 1). Use of γ- carbonyl cation precursor 2b (R\(_1\) = CO\(_2\)Me) gave good yields of condensation product 3b (76%), while substitution on the remote alkene carbon with methyl (2c) and trimethylsilyl (2d) functions also allowed formation of condensation products (3c-d) successfully (3c, 84%; 3d, 71%). Polyalkylation of the naphthalene nucleus did not appear to be a significant problem.

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Figure 1 Rearranged abietanes containing cyclohepta[de]naphthalene nucleus.
with ability was explored. The unsubstituted cyclo-
synthesis of cyclohepta[de]naphthalenes, and this possi-
tions could be effected by (NH₂)₂Ce(NO₃)₆, affording
diyne 6 in 57% yield (64% based on recovered starting
4a). Hydrogenation of the alkynes using the Lindlar
catalyst gave the diallylated naphthalene 7 (90% yield),
and subsequent ring closing metathesis using
(Cy₃P)₂Cl₂Ru=CHPh (Grubbs 1 catalyst, 5 mol%) af-
fledged. In this case, unsymmetri-
carboxylic acid (I₂, THF, 93%) to give 17 in excellent yield. After removal of the hexacar-
bondicobalt unit (I₂, THF, 93%) to give 18, catalytic hy-
drogenation (H₂, Pd/C) of the alkyne afforded 19 (94%). Hydrolysis of both the methyl ester and ace-
cate functions was rather sluggish, but in K₂CO₃/MeOH
reflux, 19 gradually was converted to phenolic acid 20
(76%). Subjecting 20 to polyphosphoric acid (CH₃Cl₂,
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diolic ring of compound 15 existed entirely in the eno-
ic/phenolic tautomer, as expected based on the existence
of 1-hydroxy-7,12-pleiadenedione in its phenolic form.¹⁰

Similarly, cyclohepta[de]naphthalene 15 was best
approached via a monocondensation route employing γ-
carboxylic cation precursor 2b. In this case, unsymmetri-
carboxylic acid (I₂, THF, 93%) to give 17 in excellent yield. After removal of the hexacar-
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As opposed to 8, other cyclohepta[de]naphthalene model
systems were best approached from 3b. For dimethyl
substituted cyclohepta[de]naphthalene 9, 3b was readily
decomplexed by I₂ in THF to give 10 in excellent yield

(98%) (Scheme 2). Catalytic hydrogenation of the alkyne
function was sluggish over Pd/C, but proceeded well
over Rh/C to afford 11 (99% yield). Subsequent addition of excess MeLi to the ester gave tertiary alcohol 13 (61% yield) along with an amount of methyl ketone 12 (25% yield). Finally, treatment of tertiary alcohol 13 with H₂SO₄ (1 drop) gave cyclohepta[de]naphthalene 9 (70% yield), contaminated with a small amount (10%) of elimination product 14.¹⁶

Scheme 1 Dihydrocyclohepta[de]naphthalene preparation from 4a via
catalytic ring closing metathesis.

<table>
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<td>H</td>
<td>4a, 5a</td>
<td>69, 9</td>
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<tr>
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<td>SiMe₃</td>
<td>3d, 5d</td>
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² Compound 2b was employed as the methyl ether
³ Reaction conducted at 0 °C – RT. In addition, 59% of 3d was iso-
lated.

Given a basic understanding of the reactivity of 2,7-
dioxygenated naphthalenes to propargylicobalt cations, we considered γ-carboxylic cation adduct 3b and 1,8-
dicondensation product 4a viable intermediates in the synthesis of cyclohepta[de]naphthalenes, and this possibility was explored. The unsubstituted cyclo-
hepta[de]naphthalene nucleus was approached beginning with 4a (Scheme 1). Decomplexation of the alkyne functions could be effected by (NH₂)₂Ce(NO₃)₆, affording diyne 6 in 57% yield (64% based on recovered starting
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Scheme 2 Conversion of 3b to 7,7-
 dimethyltetrahydrocyclohepta[de]naphthalene.

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We are grateful to NSERC (Canada), the Canada Foundation for Innovation (CFI) and Ontario Innovation Trust (OIT) for support to a conventional extractive workup. Purification by decomplexed and reduced adduct 19 was subjected to reaction with MeLi, affording tertiary alcohol 21 in 70% yield (Scheme 4). Exposure of 21 to a single drop of H$_2$SO$_4$ in CH$_2$Cl$_2$ promoted rapid cyclization at 0 °C, giving 22 in 70% yield. Compound 22 existed entirely in the dehydro- β-tetralone tautomeric structure present in microstiegol; no evidence of the enol tautomer could be observed spectroscopically. To our knowledge, this constitutes the first preparation of this ring system.

Finally, we deemed it important to determine whether the combination of the seven- membered ring system and latent carbonyl function would be sufficient to drive the naphthol ring tautomer to the keto form. To this end, decomplexed and reduced adduct 19 was subjected to reaction with MeLi, affording tertiary alcohol 21 in 70% yield (Scheme 4).

Scheme 3 Preparation of tetracyclocorhaphe[de]naphtalene-7-one.

Experimental Section

To a solution of 2,7-dimethoxyxynaphthalene 1 in CH$_2$Cl$_2$ (0.05 M) at 0 °C was added propargyl alcohol complex 2 (1.1 equiv for monocoordinations, 2.2 equiv for dicordination) and BF$_3$·OEt$_2$ (3 equiv). After 3 h of stirring at 0 °C, NH$_4$Cl(aq) was added, and the mixture subjected to a conventional extractive workup. Purification by flash chromatography afforded 3 (monocoordination) or 4/5 (dicondensation).

Acknowledgment

We are grateful to NSERC (Canada), the Canada Foundation for Innovation (CFI) and Ontario Innovation Trust (OIT) for support of this research.

References


However, substitution at the propargylic site in herc 1994.

Selected compounds:

- CO) 807.7917, found 807.7904. (6) (40) 7.75 (d, J = 8.8, 1H), 7.67 (d, J = 8.8, 1H), 7.64 (m, 2H), 7.46 (m, 2H), 4.15 (m, 2H), 3.69 (m, 2H), 3.03 (m, 2H), 2.41 (m, 2H). HERMS m/e for C13H15O5 calculated (M+) 288.1362, found 288.1360. (13) (19) (17) (V) (20)
(21) IR (KBr) \(\nu_{\text{max}}\) 3358, 2967 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 8.10 (br s, 1H), 7.65 (d, J = 8.8, 1H), 7.61 (d, J = 8.9, 1H), 7.33 (d, J = 2.2, 1H), 7.08 (d, J = 8.9, 1H), 7.01 (dd, J = 8.8, 2.2, 1 H), 3.91 (s, 3H), 2.95 (br t, J = 7.0, 2H), 2.60 (br s, 1H), 1.65 (m, 4H), 1.21 (s, 6H); \(^13\)C NMR 154.6, 154.5, 134.4, 130.3, 127.3, 124.5, 122.1, 115.6, 110.7, 105.3, 72.0, 56.4, 43.5, 29.1, 23.4, 24.3; MS m/e 274 (M\(^+\)); HRMS m/e for \(\text{C}_{17}\text{H}_{22}\text{O}_3\) calcld 274.1569, found 274.1574. (22) IR (KBr) \(\nu_{\text{max}}\) 2934, 1653, 1615 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 7.29 (d, J = 9.7, 1H), 7.13 (d, J = 8.4, 1H), 6.79 (d, J = 8.4, 1H), 5.97 (d, J = 9.7, 1H), 3.84 (s, 3H), 3.63 (s, 1H), 3.36 (m, 1H), 2.42 (m, 1H), 1.84 (m, 1H), 1.51 (m, 1H), 1.38 (m, 1H), 1.27 (m, 1H), 1.17 (s, 3H), 0.66 (s, 3H); \(^13\)C NMR 203.2, 157.7, 145.5, 140.8, 129.4, 127.9, 124.4, 123.5, 108.9, 58.3, 55.7, 43.2, 37.0, 27.4, 24.2, 21.5, 20.2; MS m/e 256 (M\(^+\)); HRMS m/e for \(\text{C}_{17}\text{H}_{20}\text{O}_2\) calcld 256.1463, found 256.1457.