Pergamon

Tetrahedron Letters 42 (2001) 5363–5365

TETRAHEDRON
LETTERS

Metathesis in the presence of a transition metal alkyne complex

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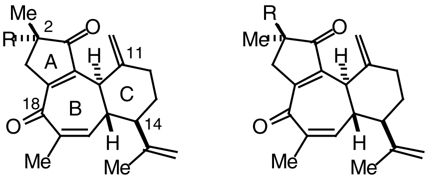
Received 11 May 2001; revised 6 June 2001; accepted 7 June 2001

Abstract—A ring closing metathesis approach to medium sized rings is described. The methodology succeeds in the presence of a transition metal alkyne complex. © 2001 Elsevier Science Ltd. All rights reserved.

The curcusones (**1**, **2**) are a family of diterpenes isolated from *Jatropha circus* that are known to enhance thermal oncotherapeutics in the Chinese hamster (Fig. 1).[1] The crystal structures of **1b** and **2a** were solved more than a decade ago, nonetheless, synthetic studies on the curcusones have only recently appeared.[2,3] Interest in developing a synthetic approach to the curcusone tricyclic framework and further assessment of potential applications in medicine led to the studies reported here.

As shown in Scheme 1, it was anticipated that **4** could be used as a building block for introduction of the A and C rings. It was projected that **4** could be assembled via metathesis of **5** in which a cobalt alkyne complex was used to link the alkene appendages.[4,5] Because cyclization to form a medium sized ring was not practical with a free alkyne as part of the ring, the metallic core in **5** was central to ring closure.[6]



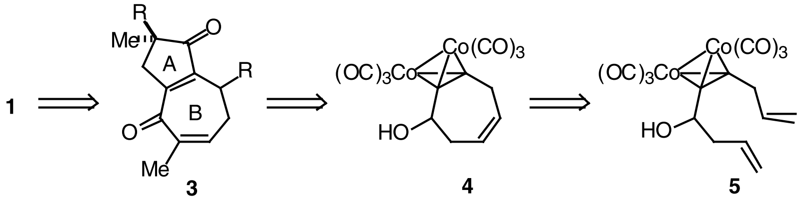
1a: R = H, curcusone A
1b: R =OH, curcusone C
2a: R = H, curcusone B
2b: R = OH, curcusone D

Figure 1. The curcusone diterpenes.

A metathesis precursor was synthesized from trimethylsilylpropynal (**6**) as outlined in Scheme 2.[7] Propynal surrogate **6** was treated with allylmagnesium bromide to afford **7**, which was desilylated under Havens' conditions to afford the known propargyl alcohol **8**.[8,9,14–16]

Conversion of **8** to the derived dianion and subsequent alkylation with allyl bromide in the presence of catalytic copper bromide·dimethylsulfide complex afforded **9**.[10] The hexacarbonyldicobalt complex of **9** proved difficult to purify, moreover, a dead end was met when **5** failed to metathesize.[11]

It was not clear whether the alcohol or organometallic group in **5** inhibited metathesis, however, the impact of internal Lewis bases on metathesis has been examined by others, primarily in the context of allylic functional-



Scheme 1. Curcusone retrosynthetic analysis.

Keywords: cyclic alkene; metathesis; dicobalthexacarbonyl alkyne complex.

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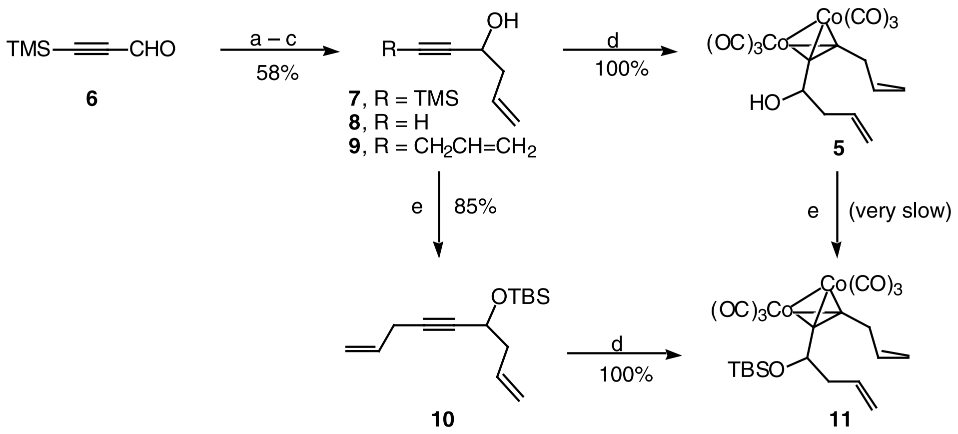
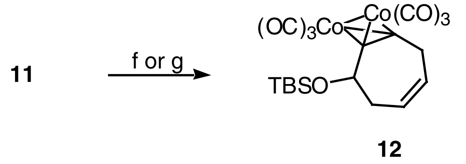
PII: S0040-4039(01)01017-6



Scheme 2. Preparation of metathesis precursor. *Reagents and conditions*: (a) CH_2=$CHCH_2MgBr$, THF; (b) KOH, MeOH, THF; (c) CH_2=$CHCH_2Br$, $CuBr{\cdot}Me_2S$, MeMgBr (2 equiv.); (d) $Co_2(CO)_8$, CH_2Cl_2; (e) TBSCl, imid.



Scheme 3. Metathesis of diene. *Reagents and conditions*: (f) $(Cy_3P)_2Cl_2Ru{=}CHPh$, CH_2Cl_2 80%; (g) 2,6-diisopropylphenylimidoneophylidenemolybdenum(VI) bis-(hexafluoro-*t*-butoxide) 63%.

ity.[12] Protection of the alcohol in **5** was undertaken, but found to be sluggish due to the proximate cobalt group. On the other hand, protection of **9** gave a high yield of the silyl ether **10**.[13] Arrival at **11** was accomplished by exposure of **10** to dicobaltoctacarbonyl (Scheme 3).[11]

In contrast to **5**, treatment of **11** with Grubbs' ruthenium alkylidene produced the cyclized curcusone building block **12** in 80% yield (Scheme 3).[4] Cyclization was evident in the 250 MHz ^{1}H NMR spectrum, where the terminal alkene signals at δ 5.88 and 5.15 in **11** collapsed to overlapping singlets at δ 5.87 and 5.78 for **12**. The use of Schrock's molybdenum catalyst also resulted in cyclization (**11**→**12**, 63%).[5]

The transformation (**11**→**12**) is an example of metal mediated formation of a medium ring, but also demonstrates that at least in some cases, preexisting organometallic groups do not interfere with metathetical ring closure.[17] The reaction suggests other sorts of organometallic complexes may be compatible with such ring forming processes.[18]

In summary, a B-ring building block for the curcusone natural products has been prepared via ring closing metathesis of an organometallic based diene. The chemistry is expected to simplify synthetic problems found in the curcusone tricyclic skeleton as well as other medium ring containing natural products. Further methodology studies and applications in synthesis are being developed, and will be reported in due course.[19,20]

Acknowledgments

The author thanks the University of Tennessee for financial assistance and a professional development award.

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19. All compounds gave satisfactory spectroscopic or combustion analysis data.
20. Selected data for new compounds: **(9)** ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 2H), 5.28 (m, 4H), 4.45 (m, 1H), 3.01 (m, 2H), 2.48 (m, 2H), 1.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 133.17, 132.22, 116.77, 116.17, 82.95, 82.28, 61.74, 42.39, 22.95; exact mass calc. for $C_9H_{12}O$ *m*/*e* 136.0888, found *m*/*e* 136.0890; **(5)** ^{1}H NMR ($CDCl_3$) δ 5.9 (m, 2H), 5.2 (m, 4H), 4.8 (m, 1H), 3.5 (m, 2H), 2.5 (m, 2H), 2.0 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 199.63, 135.68, 134.04, 116.76, 117.48, 99.91, 99.33, 71.55, 44.17, 36.24; **(10)** ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 2H), 5.25 (m, 2H) 5.11 (m, 2H), 4.40 (m, 1H), 2.98 (m, 2H), 2.41 (m, 2H), 0.90 (m, 9H), 0.11 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 134.29, 132.47, 117.35, 115.97, 83.63, 81.30, 63.01, 43.46, 25.82, 22.99, 16.25, −4.50, −5.00; exact mass calc. for $C_{12}H_{21}SiO$ (M^+–C_3H_5) *m*/*e* 209.1362, found *m*/*e* 209.1358 (M^+ was not observed); **(11)** ^{1}H NMR ($CDCl_3$) δ 5.89 (m, 2H), 5.14 (m, 4H), 4.88 (m, 1H), 3.53 (m, 2H), 2.53 (m, 2H), 0.92 (m, 9H), 0.14 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 200.20, 135.84, 133.89, 118.17, 117.24, 101.31, 96.85, 73.11, 45.18, 36.55, 25.8, 16.14, −4.15, −4.25. Anal. Calc. for $C_{21}H_{25}O_7SiCo_2$: C, 47.03; H, 4.89; found C, 46.86; H, 4.95; **(12)** ^{1}H NMR ($CDCl_3$) δ 5.83 (m, 2H), 4.88 (m, 1H), 3.64 (m, 2H), 2.35 (m, 2H), 0.94 m, 9H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 199.88, 130.26, 127.20, 103.7, 93.36, 72.60, 36.07, 33.56, 25.78, 16.08, −4.78, −4.85. Anal. Calc. for $C_{19}H_{22}O_7SiCo_2$: C, 44.90; H, 4.36; found C, 44.75; H, 4.39.