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Carene terpenoids by gold-catalyzed cycloisomerization reactions

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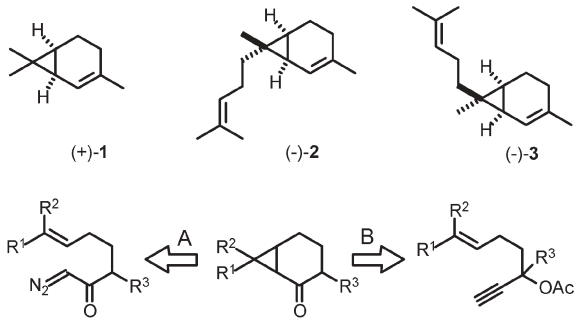
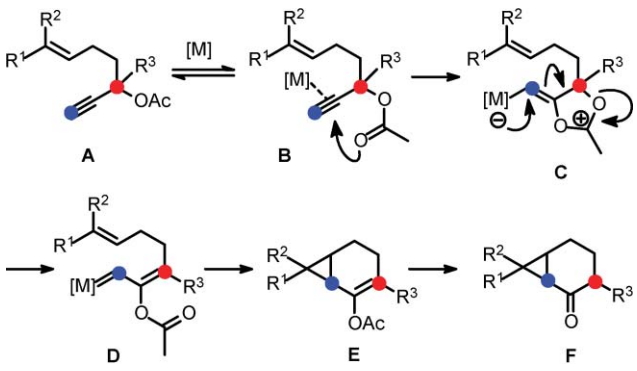
Propargyl acetates in the presence of catalytic amounts of $AuCl_3$ constitute synthetic equivalents of α-diazoketones as illustrated by a concise entry into the carene family of natural products.

A significant number of polycyclic terpenoid skeletons of varying complexity feature a cyclopropane ring. Representative examples are 2-carene **1** and its isoprenoid homologues sesquicarene **2** and isosesquicarene **3**.[1] Although many innovative syntheses of such compounds have been developed in the past,[2] the intramolecular cyclopropanation of unsaturated α-diazoketones followed by derivatisation of the resulting cyclopropyl carbonyl derivatives plays a pre-eminent role in this context (Scheme 1, path A).[3,4] As outlined below, however, this classical approach[5] may find an attractive and less hazardous equivalent in metal-catalyzed cycloisomerization reactions of readily accessible propargyl acetates (path B).

Complexation to a late transition metal cation (**A** → **B**) renders alkynes susceptible to attack by (tethered) nucleophiles such as alkenes, arenes, ethers or carbonyl groups.[6,7] If the carbonyl is part of a propargyl acetate unit, an anchimerically assisted formation of a metal carbene will ensue (**B** → **C** → **D**), which can be trapped by suitably located alkenes to form a cyclopropane ring adjacent to the incipient enol ester (**D** → **E**); hydrolysis then releases the parent cyclopropyl carbonyl derivative (**E** → **F**, Scheme 2). Although this type of rearrangement was originally discovered as a very minor side reaction in transformations mediated by $ZnCl_2$,[8] late transition metal salts turned out to be superior catalysts due to the pronounced affinity of these 'soft' cations to the π-systems of the substrate.[9–11]

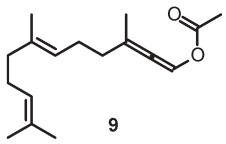


Scheme 1 Terpenes of the carene family and preparation of cyclopropyl ketones from α-diazoketones (path A) or by metal-catalyzed rearrangement of propargyl acetates (path B).



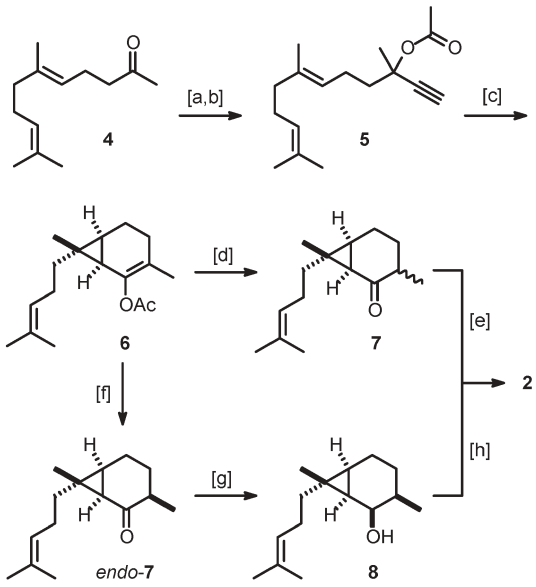
Scheme 2 Plausible mechanism for the conversion of propargyl acetates bearing tethered olefins into cyclopropyl ketones, *cf.* text.

In an attempt to scrutinize this transformation by natural product synthesis, commercial geranylacetone **4** was converted into propargyl acetate **5** in two routine steps (Scheme 3). Exposure of this compound to catalytic amounts of $PtCl_2$ in toluene, as previously recommended for rearrangements of this type,[10] resulted in the formation of the desired bicyclo[4.1.0] skeleton **6**. However, significant amounts of allenyl acetate **9**[12] formed by a [3,3]-sigmatropic rearrangement of the substrate were also detected.



Since this by-product is difficult to separate from **6** by any of the conventional methods, we chose to optimise the catalytic system further.

Amongst the host of metal salts screened,† the use of $AuCl_3$ (5 mol%)[13] in 1,2-dichloroethane at ambient temperature afforded by far the best results. Under these conditions, the expected enol ester **6** was formed in excellent yield and purity (*ca.* 95%), with only



Scheme 3 *Reagents and conditions*: [a] HC≡CMgBr, THF, 0 °C → rt, 96%; [b] Ac_2O, DMAP, Et_3N, 98%; [c] $AuCl_3$ (5 mol%), 1,2-dichloroethane; [d] K_2CO_3, MeOH, 74% (over two steps); [e] see ref. 4; [f] $LiAlH_4$, Et_2O, 0 °C → rt, 41% (over two steps); [g] L-Selectride®, THF, −78 °C → rt, 93%; [h] PPh_3, DEAD, THF, 70% (GC).

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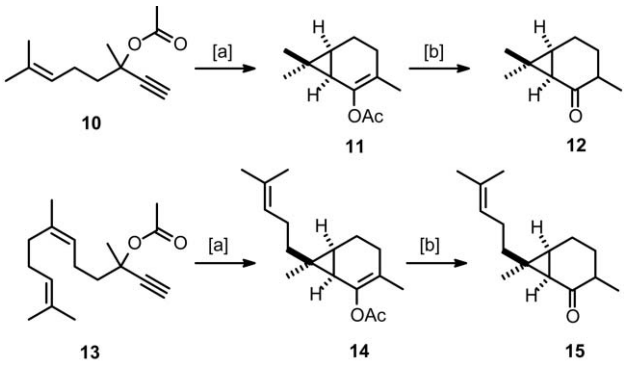

Scheme 4 *Reagents and conditions*: [a] $AuCl_3$ (5 mol%), 1,2-dichloroethane, 98% (**11**), 87% (**14**); [b] K_2CO_3, MeOH, 60% (**12**, dr = 5 : 1), 65% (**15**, dr = 4.5 : 1).

marginal amounts of allenyl acetate **9** being detectable in the crude reaction mixture. No cyclopropanation of the distal double bond of **5** was observed, thus showing that the cyclization of the conceivable 10-membered ring does not compete with the kinetically and thermodynamically more favorable formation of the sesquicarane skeleton during the $AuCl_3$-catalyzed process. Therefore it is not surprising that the truncated substrate **10** reacts equally effectively, affording product **11** in almost quantitative yield (Scheme 4).‡

Since compound **6** is rather labile, it was immediately hydrolysed with K_2CO_3 in MeOH to give sesquicarone **7** as a 6.7 : 1 mixture of diastereomers (74%, >96% pure by GC), which are known precursors to sesquicarene **2**.[4] The overall yield of **7** obtained by this novel isomerization/hydrolysis sequence is significantly higher than that of the α-diazoketone routes reported in the literature.[4] It is also interesting to note that a reductive rather than hydrolytic cleavage of the ester bond in **6** with $LiAlH_4$ in Et_2O afforded the *endo* isomer of **7** exclusively, although in somewhat lower yield (41% over cycloisomerization/reduction). Treatment of *endo*-**7** with L-Selectride® furnished alcohol **8**, which converted into **2** on treatment with PPh_3 and DEAD at ambient temperature. As previously noticed,[4] the purification of this hydrocarbon derivative requires preparative-GC.§

Next, the effect of the geometry of the reacting double bond on the outcome of the intramolecular cyclopropanation was investigated. To this end, nerylacetone was converted into propargyl acetate **13** on reaction with ethynylmagnesium bromide[15] followed by acetylation under standard conditions. Treatment of compound **13** containing a (*Z*)-configured double bond in its backbone with $AuCl_3$ (5 mol%) in 1,2-dichloroethane at ambient temperature afforded enol ester **14** which is isomeric to product **6** derived from the geranyl series (Scheme 4). Therefore it must be concluded that the Au-catalyzed skeletal rearrangement proceeds *stereospecifically*, translating the configuration of the reacting alkene into the stereochemistry of the emerging cyclopropane unit.

In summary, it is shown that the $AuCl_3$-catalyzed rearrangement of propargyl acetates constitutes an attractive alternative to the use of α-diazoketones for the preparation of cyclopropyl carbonyl derivatives and opens a stereoselective entry into various terpene derivatives belonging to the carene family. Further investigations on the use of late transition metals as selective 'π-acids' are underway and will be reported in due course.

Notes and references

† This includes the following metal salts and complexes: $PtCl_2$, $PtCl_4$, $Pt(acac)_2$, $(cod)PtCl_2$, $PtBr_2$, PtI_2, $Pt(CN)_2$, $(PhCN)_2PtCl_2$, $AgBF_4$, AgOTf, $PdCl_2$, InCl, $InCl_3$, $RuCl_3{\cdot}nH_2O$, $FeCl_3$, ZnI_2, $CoBr_2{\cdot}nH_2O$, $IrCl_3$, $NiCl_2$, $[(cod)RhCl]_2$, $[(CO)_3RuCl_2]_2$, $[(Ph_3P)AuCl]/AgSbF_6$. Solvents screened: toluene, CH_2Cl_2, 1,2-dichloroethane, DME, THF, MeCN.

‡ Representative procedure: a solution of 3,7-dimethyloct-6-en-1-yn-3-yl acetate **10** (200 mg, 1.03 mmol)[14] in 1,2-dichloroethane (10 mL) was added to a Schlenk-flask charged with $AuCl_3$ (16 mg, 0.052 mmol) under argon. After stirring for 12 h, the mixture was filtered through a pad of Celite which was carefully rinsed with hexanes–EtOAc (3 : 1). Evaporation of the combined filtrates afforded product **11** as a pale-brown syrup (197 mg, 98%, >94% pure by GC). Because this compound is fairly labile, it was immediately hydrolyzed with K_2CO_3 in MeOH to give 2-carvone **12**. Characteristic data for **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (m, 1 H), 2.16 (s, 3 H), 1.80 (m, 2 H), 1.64 (m, 1 H), 1.53 (s, 3 H), 1.09 (m, 2 H), 1.06 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 141.0, 118.6, 29.3, 27.6, 24.5, 24.2, 23.5, 20.5, 17.2, 15.6, 15.3; IR (KAP): 2918, 2865, 1753, 1698, 1449, 1367, 1208, 1165, 1097, 1044, 1009, 922, 889 cm^{-1}.

§ An efficient method for the conversion of **7** into **2** avoiding this cumbersome purification by prep-GC involves reduction of the corresponding enol triflate with a hydride donor in the presence of Pd(0). Details will be reported in a forthcoming full paper.

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