SIMPLE SYNTHESIS OF (±)-β-TRANS-BERGAMOTENE

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Summary: (±)-β-trans-Bergamotene (4) has been synthesized in five steps from geranylacetone using intramolecular ketene–olefin cycloaddition as a key step.

We have recently completed a synthesis of retigeranic acid (1)[1] in which the pentacyclic system was generated by intramolecular cycloaddition of the ketene 2 (derived from the reaction of the corresponding acid chloride with triethylamine) to form the cyclobutanone 3.[2]

| 1 | 2 | 3 |
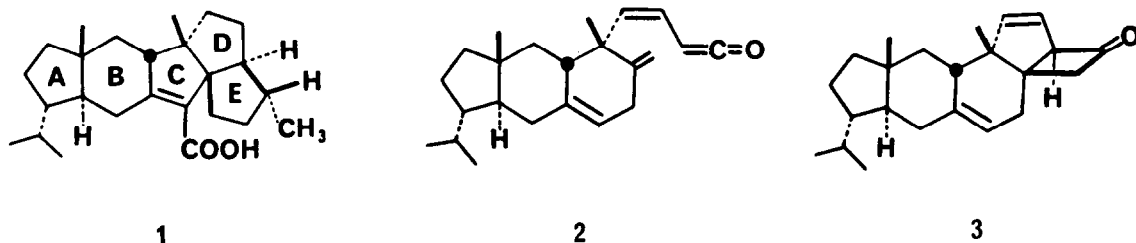
The intramolecular ketene–olefin reaction occurred smoothly at 23° in 5 min to produce selectively cyclobutanone 3 in 80% isolated yield. The intramolecular ketene–olefin cycloaddition reaction has also been studied in these laboratories with a variety of substrates in conjunction with other synthetic targets. In some cases fused-ring cyclobutanones were obtained (as for 3) but in others 1,3-bridged cyclobutanone structures were isolated. The literature also records the formation of both fused and bridged cyclobutanones from internal ketene–olefin reactions.[2]

The problem of predicting the positional selectivity ("regioselectivity") of the internal ketene–olefin cycloaddition, which is central to the effective use of this process in the synthesis of complex molecules, is strongly linked to the question of mechanism, a matter that is far from settled. A key point is the extent to which the cycloaddition involves the simultaneous formation of the two new bonds. Although synchronous pericyclic mechanisms have a substantial following,[3] there are data which together make a reasonable case for lack of concert, and specifically for a transition state in which bonding between the ketenic carbonyl carbon and one of the olefinic carbons (the most nucleophilic) is considerably advanced over the development of the second bond.[4] In our experience the asynchronous picture provides a more useful model for predicting the course of intramolecular ketene–olefin cycloaddition than do any of the synchronous

mechanisms, at least for fairly nucleophilic olefins. The smooth and efficient transformation of 2 into 3 is much more easily explained by the operation of an asynchronous pathway than by a concerted [π2s + π2a] route.[3] The rigidity of ketene 2 makes this substrate an especially discriminating test case when models of the various possible transition states are considered. In the asynchronous transition state the ketenic carbonyl carbon can strongly bond to the terminal methylene carbon (electrophilic attack in the Markovnikov sense), and from this structure the second bond of adduct 3 can smoothly be formed. Reasonable molecular geometry for the [π2s + π2a] transition state seems unattainable from 2, however.

The asynchronous transition state model leads to the expectation that a simple synthesis of β-trans-bergamotene 4 should be possible by the use of the intramolecular ketene–olefin cycloaddition as a key step. In this note we describe the study of this critical test case. The results, which are in full accord with the asynchronous model, demonstrate a remarkably short (5 steps) route to β-trans-bergamotene from the inexpensive starting material geranylacetone (5). β-trans-Bergamotene was first synthesized several years ago by a relatively lengthy route.[5]

Treatment of geranylacetone (5) in tetrahydrofuran (THF) at −78° with 2 equiv of lithium diisopropylamide selectively generated the terminal enolate which was then treated with excess dry carbon dioxide to afford after extractive isolation the β-keto acid 6[6a] as a colorless oil (83%). Reaction of 6 with excess methylenetriphenylphosphorane (generated from methyltriphenylphosphonium bromide and sodium hexamethyldisilazide) under argon in toluene at −50 to 25° over 25 hr gave the triene acid 7[6] (40%) along with 60% unchanged keto acid 6. Treatment of 7 with 3 equiv of oxalyl chloride in benzene at 25° for 2 hr followed by removal of solvent in vacuo produced the corresponding acid chloride 8 which was used for the next step directly without purification. Slow addition of a solution of 8 in toluene (by motor-driven syringe over 6 hr) to a solution of 3 equiv of diisopropylethylamine in toluene at reflux under argon generated ketene 9 which underwent cyclization to form cyclobutanone (10)[6] isolated by chromatography on silica gel in 43% yield. In addition to 10, this reaction produced the E and Z forms of 11 (15–20% yield) and more polar products (perhaps derived by ketene dimerization). Cyclobutanone 10 was converted to the corresponding hydrazone (4 equiv of hydrazine, 1 equiv of acetic acid in ethanol at 25° for 6 hr) which after extractive isolation was transformed into (±)-β-trans-bergamotene[6] (4) (70% yield) by exposure to 10 equiv of potassium t-butoxide in dimethyl sulfoxide[7] at 25° for 16 hr. The synthetic product was identified by comparison of the infrared, 270 MHz proton magnetic resonance and mass spectra with those of the naturally derived substance.[8]

β-trans-Bergamotene is of considerable interest as a biosynthetic precursor of fumagillin and ovalicin[9] and the availability of synthetic material should be helpful to further studies.

The use of the intramolecular ketene–olefin cycloaddition as a useful synthetic method for the construction of polycyclic structures has now been demonstrated for 1 and for 4; work in progress in these laboratories also has shown the effectiveness of this process for the simple synthesis of gingkolides.[10] It is clear that further systematic studies of the intramolecular ketene–olefin cycloaddition can contribute in a decisive way to the understanding of mechanism. For the time being the asynchronous cycloaddition model best accords with current information.[11,12]
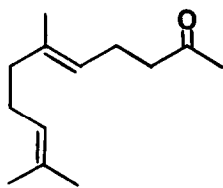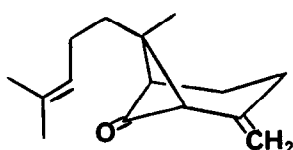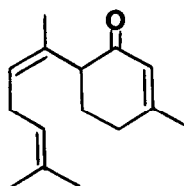
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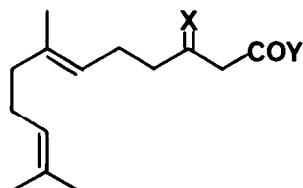
6 X = O , Y = OH
7 X = CH₂ , Y = OH
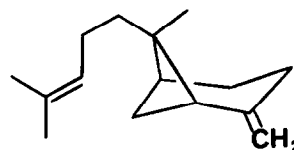**8** X = CH₂ , Y = Cl

9
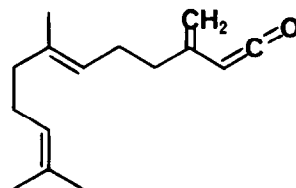
10   **11**   **4**

(+)-1-Oxo-β-trans-bergamotene (10): To a stirred solution of acid 7 (150 mg, 0.64 mmole) in 5 ml of benzene at 25° under argon was added oxalyl chloride (240 mg, 1.92 mmole). The reaction mixture was stirred (25°, 2 hr) and then benzene and excess oxalyl chloride were removed at 30 mm. The acid chloride thus obtained was dissolved in toluene (6.4 ml), and was added by motor-driven syringe over 5 hr to a stirred solution of diisopropylethylamine (250 mg, 1.92 mmole) in toluene (58 ml) maintained at reflux. The reaction mixture was further stirred at that temperature for 1 hr, cooled, and then diluted with 1N HCl (5 ml). The organic phase was washed with water, dried (MgSO₄) and concentrated under reduced pressure to give a yellow oil which was chromatographed. Elution with 5% ether in pentane gave 1-oxo-β-trans-bergamotene (10) (60 mg, 43%). ^{1}H NMR (CDCl₃, 270 MHz): δ 1.02 (3H, s), 1.4 - 1.5 (2H, m), 1.6 (3H, s), 1.67 (3H, s), 1.9 - 2.05 (2H, m), 2.05 - 2.2 (2H, m), 2.25 - 2.4 (2H, m), 2.71 (1H, dt, J=3.6, 7Hz), 3.22 (1H, d, J=7Hz), 4.64 (1H, s), 4.81 (1H, s), 5.07 (1H, t, J=6.9Hz). IR (CCl₄): 2960, 1780, 1644, 1450, 1380, 890 cm.$^{-1}$ MS (EI): 218 (M+.), 203.

(+)-β-trans-Bergamotene (4): A mixture of 10 (55 mg, 0.25 mmole), absolute ethanol (2.5 ml), anhydrous hydrazine (32 mg, 1 mmole) and acetic acid (15 mg, 0.25 mmole) was stirred at 25° for 6 hr. The reaction mixture was diluted with ether (40 ml), washed successively with 1N NaOH (5 ml) and saturated sodium chloride and then dried (MgSO₄). Evaporation of solvent afforded the hydrazone of 10 (62 mg) which was dissolved in dry DMSO (2.5 ml). Potassium t-butoxide (140 mg, 1.25 mmole) was added and the reaction mixture was further stirred for 12 hr. The mixture was poured into pentane (35 ml). The pentane layer was washed with 1N HCl (10 ml), saturated sodium chloride and dried (MgSO₄). Evaporation of pentane afforded a yellow oil which was chromatographed. Elution with pentane afforded (+)-β-trans-bergamotene (4) (35.0 mg, 69%). ^{1}H NMR (CDCl₃, 270 MHz): δ 0.71 (3H, s), 1.42 (1H, d, J=9.9Hz), 1.5 - 1.65 (2H, m), 1.62 (3H, s), 1.7 (3H, s), 1.78 - 1.86 (2H, m), 1.86 - 2.01 (2H, m), 2.01 - 2.1 (1H, bm), 2.2 - 2.35 (2H, m), 2.45 - 2.65 (2H, m), 4.56 (1H, s), 4.63 (1H, s), 5.16 (1H, t, J=7.8Hz). IR (FT, film): 2922, 1641, 1450, 1376, 875 cm.$^{-1}$. MS (EI): 204 (M+), 161, 133, 109.

References and Notes

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