New reactions and step economy: the total synthesis of (±)-salsolene oxide based on the type II transition metal-catalyzed intramolecular [4 + 4] cycloaddition

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Abstract:
Studies on the viability of the type II nickel-catalyzed intramolecular [4+4] cycloaddition of bis-dienes show that it is influenced by both diene substitution and geometry. Both *E*- and *Z*-isomers of 19 and 20 react, albeit at markedly different rates, to afford cycloadducts, whereas only the *Z*-isomer of 9 (and not the E-isomer) reacts to give 8 and 25. Chemoselective elaboration of 8 to (±)-salsolene oxide (7) was used to confirm the cycloadduct structure while establishing a step economical route to the natural product.

Article:
1. Introduction
Step economy is a preeminent goal of organic synthesis.[1] It influences the length, efficiency, cost, development time, execution time, effort, separation science, and environmental impact of a synthesis and therefore its capacity to efficaciously deliver a meaningful supply of target. Step economy is in turn influenced by reaction selection and is generally favored by the use of reactions that allow the greatest increase in target relevant complexity.[2] The ability to access more complex targets with step economy is thus principally deter-mined and limited by the lexicon of known organic reactions (Fig. 1). The introduction of new reactions is thus a critical if not unique requirement for extending the reach of contemporary synthesis and thereby its impact on fundamental and applied aspects of chemistry, biology, medicine, materials, and environmental sciences.
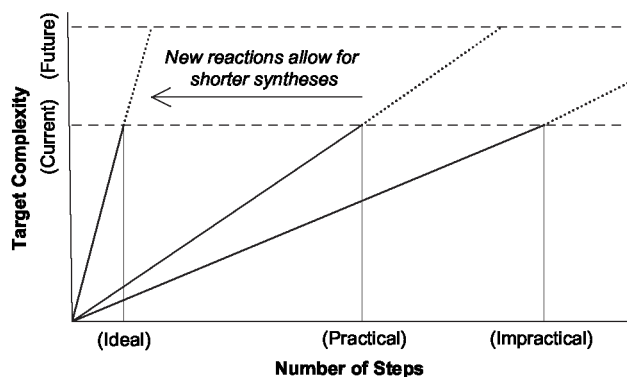

Figure 1. The relationship of step economy to complexity and new reactions.

Prompted by the above considerations, we have focused effort on the design or discovery of novel or new reactions[3] that provide fundamentally new ways of accessing ring systems commonly encountered in natural and designed poly-cyclic targets. A special emphasis has been placed on reactions that in the absence of catalysts are forbidden or difficult to achieve. Following the pioneering work of Reppe,[4] Reed,[5] Wilke,[6] and others,[7] we reported early on in this series the first examples of the intramolecular, metal-catalyzed [4+4] cycloaddition of bis-dienes.[8,9] As a consequence of its intramolecularity, this reaction allows for control over selectivity and for the introduction of substituents that are not possible with its intermolecular counterpart.
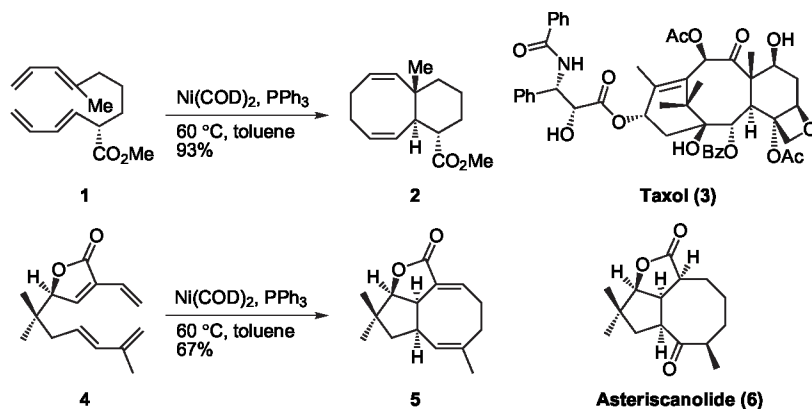
Scheme 1. Representative examples of type I metal-catalyzed [4+4] cycloadditions.

This process has been used to readily access the fused eight-membered ring core of taxol (3)[10] and of asteriscanolide (6: Scheme 1).[11] The use of this cycloaddition to access bridged bicycles containing an eight-membered ring as are found in various natural products[12] has in contrast received little attention.[13] We report herein an exploratory mechanistic study on the utility of the type II intramolecular nickel(0)-catalyzed [4+4] cycloaddition for the synthesis of bicyclo[5.3.1]unde-cane derivatives, the influence of diene geometry and substitution on the type II process, and the preliminary application of this type II process to the total synthesis of (±)-salsolene oxide (7: Scheme 2).
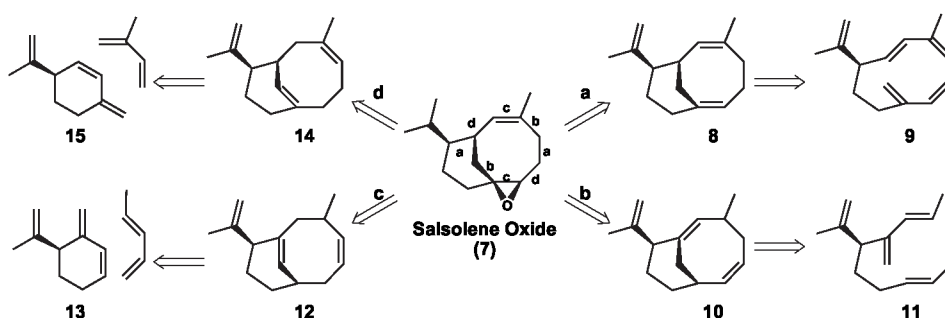
**Scheme 2.** Connectivity analyses of salsolene oxide using a type II [4+4] cycloaddition.

2. Results and discussion

Salsolene oxide (7) is a tricyclic sesquiterpene reported by Weyerstahl in 1991 as an isolate of the Himalayan plant *Artemisia salsoloides*.[14] Its synthesis has been reported by Paquette and coworkers and entails an impressive 16-step route in which (*R*)-(—)-carvone is cleaved to an acyclic bromoester, which is then converted using a [2+2] cyclo-addition to a bicyclo[3.1.1]heptanone. The bicyclo[5.3.1]un-decenone core structure of the target is then derived through a ring expansion of a four- to an eight-membered ring.[15]

In considering a synthesis of salsolene oxide (7: Scheme 2), one is confronted with the task of assembling its bicyclo[5.3.1]undecane ring system, also found in taxanes and other natural products,[12] along with an uncommonly encountered bridgehead epoxide. Connectivity analysis 16 suggests four general ways in which this ring system could be assembled using a [4+4] cycloaddition strategy: connections of paired-bonds labeled a, b, c, or d (Scheme 2). The two intermolecular options (c and d) are excluded on mechanistic grounds as they would require formation of a highly strained bridgehead alkene. The intramolecular strategies using a type II [4+4] cycloaddition (a and b) are not without concerns as well as they too would lead to cycloadducts with bridgehead alkenes, albeit ones which would be less strained. If successful, however, route a would afford several important synthetic advantages. It positions all of the alkenes in the cycloadduct in exactly the locations needed for accessing the target functionality, offering an advantage over the other type II process (route b). Moreover, the three alkenes in cycloadduct 8 would be expected to exhibit differentiated reactivity. The more reactive bridgehead alkene would be expected to undergo epoxidation with chemo-and diastereoselectivity to provide the bridgehead epoxide of the target allowing then for selective reduction of the sterically less encumbered isopropenyl pi-system. In addition, the required bis-diene precursor 9 could be assembled readily from commercially available building blocks (Scheme 3). Ten carbons would come from the monoterpene

myrcene (16), one from acetate, and four from methacrolein. The simplicity and brevity of this plan are a direct and unique consequence of the value of new strategy level reactions,[2a] in this case the type II [4+4] cycloaddition, as tools for achieving step economical syntheses.

The synthesis of the tethered bis-dienes (9, 19, and 20: Scheme 3) required for testing the viability of this type II [4+4] process (route a: Scheme 2) began with the previously reported Büchi–Sharpless oxidation of commercially avail-able myrcene (16) to myrcenol.[17] Conversion of the latter to its acetate 17 (88%) followed by Ireland–Claisen re-arrangement[18] provided carboxylic acid 18 in 77% yield. The second diene subunit was then introduced through a two-step procedure involving condensation of the dianion of 18 individually with methacrolein, acrolein, or methyl-vinylketone, and subsequent decarboxylative dehydration of each resulting hydroxy acid to afford bis-dienes 9 (*E*-isomer only), 19 (*E*:*Z*=1: 1), and 20 (*E*:*Z*=3:1) in comparable overall yields (40–50%). This strategy serves as an expedient and general route to the bis-dienes required for type II [4+4] cycloadditions.
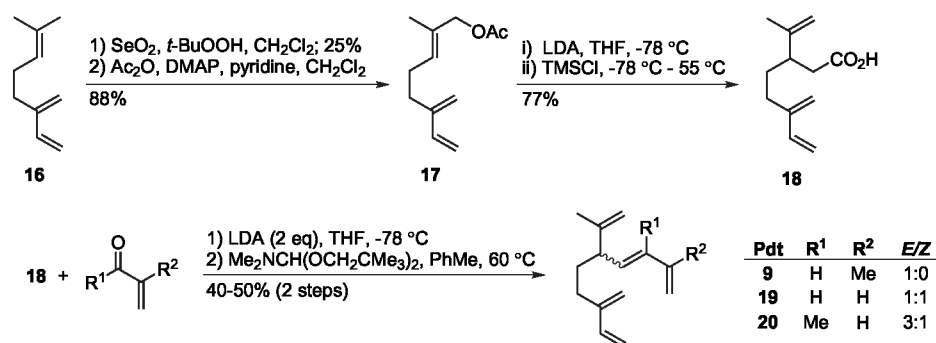

Scheme 3. Synthesis of the bis-diene precursors for type II [4+4] cycloadditions.

The viability of the key type II [4+4] cycloaddition was explored using various catalysts, ligands, and solvents with substrates 9, 19, and 20. An effective procedure involved treatment of the bis-dienes 19 (*E*/*Z*=1:1) with Ni(COD)$_2$ (10 mol %) and P(*O-o*-biph)$_3$ (30 mol %) in toluene at 85 °C, which provided cycloadducts 21 and 22 (4: 1) in 67% yield (Scheme 4). For comparative purposes, reaction of the 3-methyl substituted bis-dienes 20 (*E*:*Z*= 1.4: 1) was conducted under similar conditions and gave the cycloadduct 23 although in lower yield (36%). While unoptimized, these results offered encouragement for the viability of the key cycloaddition involving bis-diene *E*-9. Rather remarkably, however, when 2-methyl substituted bis-diene *E*-9, the potential precursor to salsolene oxide, was subjected to the above conditions, intramolecular cycloaddition did not occur. At extended reaction times, only intermolecular [4+4] cycloadducts formed slowly. Changes in solvent (THF and toluene), ligand (phosphines and phosphites), and metal-to-ligand ratios (from 1: 1 to 1:3) did not alter this outcome. While the effect of substitution on the diene is of general mechanistic interest, the absence of type II cycloadducts in the reaction of *E*-9 presented a significant problem with respect to the specific application of this reaction to the synthesis of salsolene oxide.
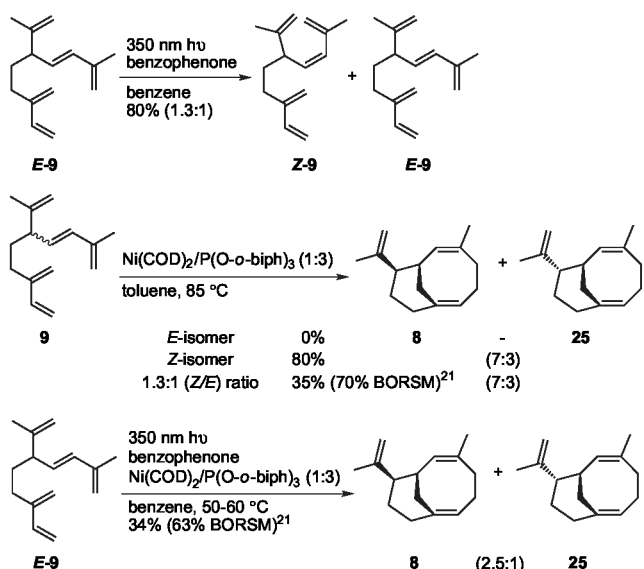
In our previous studies on nickel-catalyzed [4+2] cycloadditions, we observed that *E*- and *Z*-diene isomers reacted at different rates,[19] suggesting a potential solution to the above problem involving *E*-9. To address this point and to establish a more detailed analysis of the time course of these reactions, the cycloadditions of 19 and 20 were monitored by gas chromatography. As observed in [4+2] cycloadditions, the *Z*-isomers of 19 and 20 underwent [4+4] cycloaddition more rapidly than the E-isomers, reacting readily even at lower temperatures (60 °C). Typically, at 85 °C in the presence of Ni(COD)$_2$ (25 mol %) and P(*O-o*-biph)$_3$ (75 mol %) in toluene, *Z*-19 was consumed completely within 25 min, during which time less than 20% of the corresponding *E*-19 had reacted. Complete conversion of the latter required 5–6 h. Similar results were obtained for 20; the Z-isomer was consumed in 2 h while the *E*-isomer required excess of 12 h for complete conversion.

Guided by these encouraging results, a study of the behavior of *Z*-9 was conducted. For this purpose, *E*-9 was photoequilibrated (Rayonet reactor, 350 nm) in benzene in the presence of benzophenone as a sensitizer (10 mol %) to provide a 1.3:1 mixture of *Z*-9 and *E*-9 (80% yield) from which the *Z*-isomer could be obtained by

chromatographic purification. In contrast to the behavior of *E*-9, when *Z*-9 was subjected to typical reaction conditions cycloadducts 8 and 25 (7:3) were obtained in 80% yield (Scheme 5). In accord with the above stereochemical effects, when mixtures of *Z*-9 and *E*-9 were submitted to these reaction conditions, the Z-isomer was completely consumed in 10 min at 80 °C while the *E*-isomer remained unchanged. This striking difference in reactivity allowed convenient recycling of the unreactive isomer by photo-equilibration, thereby increasing the overall throughput of this route to salsolene oxide. Significantly, both processes, an in situ photo-equilibration and the [4+4] cycloaddition, could be achieved in one operation. This unoptimized procedure allowed the more reactive bis-diene isomer (*Z*-9) to be siphoned off through a [4+4] cycloaddition. A direct synthesis of the Z-isomer was not pursued as this photo-equilibration–cycloaddition process served to address both the mechanistic and strategic proof of concept goals of this initial study.

9,19,20	R¹ = H, R² = H	67%	(4:1) (21:22)
	R¹ = Me, R² = H	36%	(>10:1) (23:24)
	R¹ = H, R² = Me	0%	
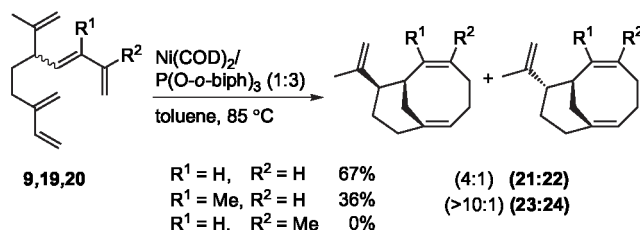
Scheme 4. Initial results of the type II [4+4] cycloaddition.

9	*E*-isomer	0%	8	-	25
	Z-isomer	80%		(7:3)	
1.3:1 (*Z/E*) ratio	35% (70% BORSM)[21]			(7:3)	

Scheme 5. Serial photoisomerization and [4+4] reaction of **9**.
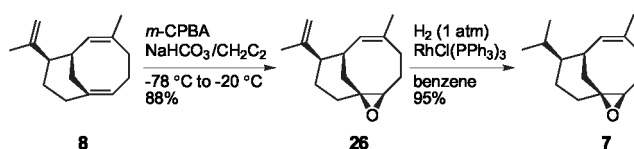
Scheme 6. Completion of the synthesis of (±)-salsolene oxide.

Chemoselective mono-epoxidation of triene 8 was achieved with m-CPBA at -78°C to -20°C to provide the desired epoxide 26 in 88% yield (Scheme 6). The presence of solid sodium bicarbonate in this reaction serves to suppress an acid-catalyzed rearrangement of the desired product. Finally, chemoselective hydrogenation of diene 26 was accomplished with Wilkinson's catalyst, providing salsolene oxide (7) in 95% yield.

3. Conclusion

The type II [4+4] cycloaddition has been shown to be a powerful tool in the synthesis of bicyclo[5.3.1] undecadienes, the core of a number of important natural products. An initial mechanistic study, examining the effects of substitution and alkene geometry on the cycloaddition, showed that both factors influence the reaction outcome. The most remarkable illustration of this influence was with the *E*- and *Z*-isomers of 9, the former being unreactive while the latter reacting in high yield to provide bicyclo[5.3.1]undecadiene cycloadducts 8 and 25. The use of a novel serial photoisomerization–cycloaddition process allowed the unreactive E-isomer to be photoequilibrated with the reactive *Z*-isomer and the latter to be siphoned off through a type II [4+4] cycloaddition. Type II cycloadduct 8 was converted to (±)-salsolene oxide (7) in two chemoselective steps. The value of new complexity increasing reactions in achieving step economical syntheses is suggested in part by the reduction in total step count (16–8 steps) made possible with this novel type II [4+4] cycloaddition.[15]

4. Experimental

4.1. Myrcenol

To a solution of myrcene (16, 35.6 g, 0.26 mol) in 250 mL CH_2Cl_2 was slowly added a mixture containing SeO_2 (14.3 g, 0.13 mol), 60 mL of a 90% aqueous t-butylhydro-peroxide solution and an additional 150 mL CH_2Cl_2. During this period the reaction temperature was carefully controlled not to exceed 10 °C. After an additional 4 h at 10 °C, the re-action mixture was brought to room temperature and stirred overnight. Benzene was added to the reaction mixture and CH_2Cl_2 was removed in vacuo. The remaining benzene solution was diluted with Et_2O and washed twice with 10% aqueous NaOH and three times with a 10% aqueous $NaHSO_3$ solution, followed by washing with brine and drying with $MgSO_4$. After removal of the combined organic solvents in vacuo, the crude material was dissolved in methanol, cooled to 0 °C, and treated with an excess $NaBH_4$ (5 g) in small portions. After stirring overnight at room temperature the reaction mixture was hydrolyzed with a saturated aqueous NH_4Cl solution. Extraction with Et_2O, drying with $MgSO_4$, filtration, and concentration in vacuo gave crude myrcenol, which was purified via flash chromatography (SiO_2; hexane/ethyl acetate = 9:1 (v/v)). After purification 10.7 g (0.0703 mol, 25%) myrcenol was obtained as a color-less oil.

Spectral data matched that of the known compound.[17a]

4.2. Acetate 17

Myrcenol (8.8 g, 58 mmol) was dissolved in 50 mL dry pyridine. Acetic anhydride (11.8 g, 112 mmol) and a catalytic amount of DMAP (5.8 mmol) were added. The reaction mixture was stirred at 0 'C overnight. Removal of the solvent in vacuo, followed by flash chromatography (SiO2; hexane/ethyl acetate 1/4 9:1 (v/v)) gave 9.9 g (51 mmol, 88%) of the acetate as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): 6.38 (dd, J=17.6, 11.0 Hz, 1H); 5.52–5.50 (m, 1H); 5.26 (d, J=17.6 Hz, 1H); 5.08 (d, J=11.0 Hz, 1H); 5.04 (s, 1H); 5.00 (s, 1H); 4.47 (s, 2H); 2.27 (br s, 4H); 2.10 (s, 3H); 2.08 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 170.9, 145.6, 138.7, 130.6, 129.1, 115.9, 113.1, 70.1, 30.8, 26.3, 21.0, 13.9. IR (thin film): v 3089 (m); 2934 (m); 1741 (s); 1596 (m); 1458 (m); 1376 (m); 1232 (s); 1023 (s) cm^{-1}. MS (70 eV): m/z (%) 159 (4); 135 (16); 119 (87); 93 (100); 92 (26); 91 (45); 79 (42).

4.3. Carboxylic acid 18

To a solution of diisopropylamine (3.5 g, 34.1 mmol) in 50 mL THF was added n-BuLi in hexane (14.2 mL of a 2.5 M solution, 35.5 mmol) at 0 °C. After 20 min at 0 °C the solution was cooled to -78 °C and a precooled solution (-78 °C) of acetate 17 (4.73 g, 24.4 mmol) in 50 mL THF was added slowly via cannula transfer. The reaction mixture was stirred at -78 °C for 20 min followed by adding chlorotrimethylsilane (3.7 g, 29 mmol, freshly distilled from CaH) in one batch. The reaction mixture was brought to room temperature and then refluxed for 5 h. After cooling, 10 mL methanol was added, followed by adding 1 g LiOH and 20 mL water. The resulting mixture was stirred overnight, concentrated, diluted with water, and extracted with Et_2O (2 x 10 mL). The aqueous layer was acidified with 1 N HCl and extracted several times with Et_2O, followed by washing with brine. The combined organic fractions were dried with $MgSO_4$ and concentrated in vacuo. Purification of the crude material by filtration through a plug of SiO_2 (hexane/ethyl acetate 1/4 1: 1 as eluent) yielded 3.66 g (18.9 mmol, 77%) carboxylic acid 18 as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.36 (dd, J=17.6, 10.8 Hz, 1H); 5.20 (d, J=17.6 Hz, 1H); 5.05 (d, J=10.8 Hz, 1H); 5.00 (s, 1H); 4.99 (s, 1H); 4.84 (s, 1H); 4.81 (s, 1H); 2.62 (m, 1H); 2.42–2.45 (m, 2H); 2.14 (m, 2H); 1.70 (s, 3H); 1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0,146.0, 145.5, 138.8, 115.8, 113.1, 112.6, 43.3, 39.0, 31.4, 28.9, 18.7. IR (thin film): v 3078 (s); 2932 (s); 1707 (s); 1644 (m); 1597 (m); 1440 (m); 1409 (m); 1293 (m) cm^{-1}. HRMS: calcd for $C_{12}H_{18}O_2$ 194.1306, found 194.1308.

4.4. General preparation of bis-dienes

A solution of lithium diisopropylamine in THF was prepared by adding n-BuLi (15.5 mL of a 2.4 M solution in hexane, 37.1 mmol) to diisopropylamine (3.75 g, 37.1 mmol) in 100 mL abs THF at 0 °C. To this freshly prepared solution was added acid 18 (3.0 g, 15.4 mmol) in 50 mL THF. The complete generation of the desired

dianion was ensured by warming the resulting mixture to 50 °C. After 1.5 h the reaction was cooled down to -78 'C and freshly distilled methacrolein (1.8 g, 26 mmol, distilled over $CaSO_4$) was added and the mixture stirred overnight. Water was added to the reaction and the THF removed in vacuo. The crude β-hydroxy acid was obtained after acidifying with 1 N HCl, extracting with Et_2O, drying the combined organic layers with $MgSO_4$, and washing with brine, followed by filtration and removal of the organic solvent in vacuo.

The crude β-hydroxy acid was dissolved in 200 mL toluene and *N,N*-dimethyl-dineopentylketal-formamide (10 mL, 8.29 g, 36 mmol) and pyridine (0.5 mL) were added. The reaction mixture was heated to 60 °C for 1 h while a slight evolution of CO_2 was visible. When complete conversion was reached (TLC) the solution was concentrated in vacuo and acidified with 0.5 N HCl. Extraction with Et_2O, washing with brine, drying with $MgSO_4$, filtration, and evaporation of the combined fractions were followed by flash chromatography (SiO_2, hexane) yielding bis-diene *E*-9 (1.3 g, 6 mmol, 40%).

4.4.1. Bis-diene *E*-9.^{1}H NMR (300 MHz, $CDCl_3$): δ 6.4 (dd, *J*=17.6, 11.0Hz, 1H); 6.18 (d, *J*=15.7Hz, 1H); 5.57 (dd, *J*=15.7, 8.0 Hz, 1H); 5.22 (d, *J*=17.6 Hz, 1H); 5.06 (d, *J*=11.0 Hz, 1H); 5.02 (m, 2H); 4.92 (br s, 2H); 4.80 (br s, 2H); 2.75 (m, 1H); 2.19 (m, 2H); 1.85 (s, 3H); 1.71 (s, 3H); 1.89–1.61 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 146.4, 142.0, 138.9, 133.0, 132.8, 115.7, 115.0, 113.2, 110.7, 50.3, 31.6, 29.2, 20.1, 18.7. IR (thin film): *v* 3081 (m); 2969 (m); 2937 (s); 1786 (w); 1734 (w); 1644 (m); 1595 (m); 1452 (m); 1438 (m); 991 (m); 966 (s)cm^{-1}. HRMS: calcd for $C_{15}H_{22}$ 202.1721, found 202.1719.

4.4.2. Bis-diene *E*-19 (isolated as a mixture of *E*- and *Z*-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27–6.42 (m, 2H); 6.08 (dd, *J*=15.0, 10.4 Hz, 1H); 5.65 (dd, *J*=8.0, 15.0Hz, 1H); 5.22 (d, *J*=17.6Hz, 1H); 5.13 (d, *J*=16.8 Hz, 1H); 5.05 (d, *J*=11.0 Hz, 1H); 5.00–5.02 (m, 3H); 4.79 (br s, 2H); 2.74 (q, J=7 Hz, 1H); 2.20 (m, 2H); 1.60–1.80 (m, 2H); 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 146.3, 138.8, 137.2, 137.1, 131.1, 115.7, 115.5, 113.2, 110.9, 50.0, 31.2, 29.2, 20.0. IR (thin film): *v* 3086 (w); 2925 (s); 2854 (m); 1797 (w); 1738 (w); 1643 (m); 1452 (m); 1375 (w); 1248 (w); 1003 (m) cm^{-1}. HRMS: calcd for $C_{14}H_{20}$ 188.1565, found 188.1565.

4.4.3. Bis-diene *Z*-19 (isolated as a mixture of *E*- and *Z*-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (m, 1H); 6.35 (m, 1H); 6.09 (dd, *J*=11.0, 9.0Hz, 1H); 5.34 (dd, *J*= 11.0, 11.0 Hz, 1H); 5.00–5.20 (m, 6H); 4.78 (br s, 2H); 3.18 (m, 1H); 2.10–2.30 (m, 2H); 1.60–1.80 (m, 2H); 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4,146.2, 138.8, 134.8, 132.2, 129.8, 117.7, 115.7, 113.2, 110.3, 45.0, 32. 1, 29.1, 20.4. See Section 4.4.2 for IR and HRMS data.

4.4.4. Bis-diene *E*-20 (isolated as a mixture of *E*- and *Z*-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (m, 2H); 5.40 (d, *J*=9.6 Hz, 1H); 5.21 (d, *J*=17.6 Hz, 1H); 5.13 (d, *J*= 17.3 Hz, 1H); 5.06 (d, *J*= 11.0 Hz, 1H); 5.00 (m, 3H); 4.70 (br s, 2H); 3.05 (m, 1H); 2.16 (m, 2H); 1.50–1.70 (m, 2H); 1.78 (d, J=1.2 Hz, 3H); 1.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 146.3, 141.6, 138.9, 135.5, 134.5, 115.7, 113.2, 111.1, 110.3, 45.6, 32.2, 29.2, 20.3, 12.1. IR (thin film): *v* 3088 (m); 2979 (m); 2940 (s); 2863 (m); 1642 (m); 1595 (s); 1441 (m); 1373 (m) cm^{-1}. HRMS: calcd for $C_{15}H_{22}$ 202.1721, found 202.1714.

4.4.5. Bis-diene *Z*-20 (isolated as a mixture of *E*- and *Z*-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (dd, *J*=17.5, 10.8 Hz, 1H); 6.38 (m, 1H); 4.90–5.40 (m, 7H); 4.78 (br s, 2H); 3.15 (m, 1H); 2.16 (m, 2H); 1.50–1.70 (m, 2H); 1.87 (s, 3H); 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 141.5, 138.8, 133.8, 133.4, 132.8, 115.7, 114.0,113.2,110.1,44.5, 32.4,29.2, 20.3,20.0. See Section 4.4.4 for IR and HRMS data.

4.5. *Photochemical isomerization of bis-diene E-9*
Bis-diene *E*-9 (200 mg, 1.0 mmol), benzophenone (18 mg, 0.1 mmol), and dodecane (200 mg, internal standard) were dissolved in 200 mL benzene. The resulting solution was purged with argon for 0.5 h followed by irradiation with 350 nm light (Rayonett photoreactor). The photochemical induced *E/Z*-equilibration was followed by GC and stopped when an *E/Z*-ratio of 1.3: 1.0 was reached. Evaporation of the solvent and filtration through a plug of SiO_2 (hexane) gave 80% of the bis-diene isomers E-9 and Z-9.

4.5.1. Bis-diene Z-9.
^{1}H NMR (300 MHz, CDCl$_3$): δ 6.37 (dd, *J*=17.6, 10.7 Hz, 1H); 5.94 (d, *J*=11.5 Hz, 1H); 5.34 (dd, *J*= 11.5, 11.0 Hz, 1H); 5.21 (d, *J*= 17.6 Hz, 1H); 5.05 (d, *J*=10.7 Hz, 1H); 5.01 (br s, 1H); 4.99 (br s, 1H); 4.95 (br s, 1H); 4.88 (br s, 1H); 4.77 (br s, 2H); 3.32 (m, 1H); 2.2 (m, 2H); 1.89 (s, 3H); 1.73 (s, 3H); 1.6–1.9 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 148.1, 146.4, 141.6, 13 8.9, 133.6, 131.4, 115.6, 115.4, 113.1, 110.4, 45.2, 32.8, 29.2, 23.3, 20.3. IR (thin film): *v* 3081 (m); 2939 (s); 1644 (m); 1595 (m); 1452 (m); 1373 (m) cm^{-1}.

4.6. General procedure for the [4 + 4] cycloaddition

To a 100 mL Schlenk flask were added bis-dienes *E*-9 and *Z*-9 (1.3:1 ratio, 47 mg, 0.223 mmol), toluene (70 mL), dodecane (47 mg, internal standard), and P(*O*-*o*-biph)$_3$ (96.8 mg, 0. 180 mmol) under an atmosphere of argon. The flask was heated to 60 °C and Ni(COD)$_2$ (0.8 mL of a 0.07 M stock solution) was added via syringe, and the flask was sealed. The dodecane/bis-diene ratio was determined and its conversion monitored by GC. After 4 h the conversion of Z-bis-diene Z-9 was complete and the reaction was stopped via cooling and exposure to air. Filtration of the toluene solution through a plug of silica and elution with Et$_2$O removed the nickel salts. Concentration in vacuo was either followed by another cycle of irradiation–Ni(0)-cyclization or by flash chromatography (SiO$_2$, hexane). An effective separation of the stereoisomers 8 and 25 was achieved with a long chromatographic column (typically 90 cmx 2.5 cm for a 100 mg sample). For mechanistic purposes all trace bis-dienes and 1,3-diene containing side products could be removed from the product mixture prior to flash chromatography by treatment with tetracyanoethene, added in excess at room temperature to a solution of the crude product mixture in CH$_2$Cl$_2$ followed by stirring for several minutes. All 1,3-diene containing materials were converted to highly polar products and were easily removed from the nonpolar products 8 and 25 with flash chromatography.

4.6.1. Cyclooctadiene 8.
^{1}H NMR (300 MHz, CDCl$_3$): δ 5.24 (dd, *J*=8.3, 2.5 Hz, 1H); 5.11 (br s, 1H); 4.97 (d, *J*=1 Hz, 1H); 4.92 (br s, 1H); 3.06 (m, 1H); 2.93 (br s, 1H); 2.84 (dt, *J*=13.0, 2.0 Hz, 1H); 2.4 (m, 1H); 2.25 (m, 1H); 2.11 (m, 1H); 1.77 (s, 3H); 1.73 (br s, 3H); 1.65–2.10 (m, 6H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 147.4, 142.6, 133.8, 130.5, 118.1, 111.6, 48.3, 41.2, 35.2, 31.8, 30.8, 30.3, 27.8, 25.1, 23.3. IR (thin film): *v* 2930 (s); 1642 (m); 1495 (m); 1444 (m); 1006 (m) cm^{-1}. HRMS: calcd for C$_{15}$H$_{22}$ 202.1721, found 202.1719. Anal. Calcd for C$_{15}$H$_{22}$: C, 89.04%; H, 10.96%. Found: C, 89.00%; H, 10.85%.

4.6.2. Cyclooctadiene 25.
^{1}H NMR (300MHz, CDCl$_3$): δ 5.26 (dd, *J*=8.4, 2.7 Hz, 1H); 5.02 (br s, 1H); 4.86 (d, *J*=1.4 Hz, 1H); 4.63 (s, 1H); 3.24 (m, 1H); 3.04 (m, 1H); 2.94 (br s, 1H); 2.42 (m, 1H); 1.95–2.22 (m, 4H); 1.69– 1.83 (m, 3H); 1.77 (s, 3H); 1.70 (t, *J*=1.9Hz, 3H); 1.49 (ddd, *J*=24.8, 12.5, 4.9Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 147.2, 141.5, 134.0, 123.5, 118.6, 110.2, 49.8, 39.9, 37.2, 36.4, 32.2, 31.5, 27.3, 24.6, 22.7. IR (thin film): *v* 2964 (s); 2928 (s); 2875 (m); 2844 (m); 1642 (m); 1495 (w); 1439 (m); 1374 (w); 1058 (w); 1017 (w) cm^{-1}.

4.6.3. Cyclooctadiene 21.
^{1}H NMR (300 MHz, CDCl$_3$): δ 5.49 (m, 1H); 5.37 (d, *J*=11.3 Hz, 1H); 5.28 (m, 1H); 4.97 (br s, 1H); 4.95 (br s, 1H); 3.00 (br s, 1H); 2.85 (m, 2H); 2.47 (m, 1H); 2.27 (t, *J*=11.0Hz, 1H); 2.16 (br s, 1H); 1.92–2.10 (m, 5H); 1.78 (s, 3H); 1.70 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 146.8, 142.0, 136.7, 126.4, 118.1, 111.2, 47.0, 42.1, 34.6, 30.4, 29.9, 26.8, 25.7, 22.8. IR (thin film): *v* 2934 (s); 1641 (m); 1456 (m); 1024 (m) cm^{-1}. HRMS: calcd for C$_{14}$H$_{20}$ 188.1565, found 188.1566.

4.6.4. Cyclooctadiene 22.
^{1}H NMR (300MHz, CDCl$_3$): δ 5.48 (m, 1H); 5.27 (m, 2H); 4.86 (d, *J*=1.3 Hz, 1H); 4.63 (s, 1H); 3.2 (dt, *J*=7.0, 3.0 Hz, 1H); 2.92 (m, 1H); 2.47 (m, 1H); 1.70–2.30 (m, 7H); 1.77 (s, 3H); 1.51 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 147.0, 141.5, 130.5, 127.1, 118.8, 110.2, 49.2, 41.2, 37.3, 36.2, 31.7, 27.4, 25.6, 22.8. IR (thin film): *v* 3008 (m); 2932 (s); 2875 (s); 1643 (m); 1492 (m); 1440 (m); 1375 (m); 1038 (w); 999 (w) cm^{-1}. HRMS: calcd for C$_{14}$H$_{20}$ 188.1565, found 188.1564.

4.6.5. Cyclooctadiene 23.
^{1}H NMR (300 MHz, CDCl$_3$): δ 5.43 (m, 1H); 5.27 (dd, *J*=7.0, 3.0 Hz, 1H); 4.97 (d, *J*= 1.4 Hz, 1H); 4.96 (br s, 1H); 2.98 (dd, *J*= 13.0, 1.7 Hz, 1H); 2.89 (m, 2H); 2.29–2.51 (m, 3H); 1.85–2.10 (m, 5H); 1.77 (s, 3H); 1.74 (s, 3H); 1.55 (m, 1H). ^{13}C NMR (75MHz, CDCl$_3$): δ 147.4, 141.8, 139.5, 123.9, 118.5,

111.3, 45.4, 43.1, 34.3, 30.1, 29.6, 27.8, 26.6, 25.1, 22.7. IR (thin film): v 3025 (m); 2964 (s); 2934 (s); 2887 (s); 1641 (m); 1497 (m); 1376 (m); 1184 (w); 1099 (w); 1023(m); 888 (m)cm^{-1}. HRMS: calcd for $C_{15}H_{22}$ 202.1721, found 202.1729.

4.7. Photochemical and Ni(0)-catalyzed formation of 8 and 25

Isomerically pure *E*-9 (49 mg, 0.243 mmol) was dissolved in 70 mL benzene and dodecane (54 mg, internal standard), benzophenone (14 mg, 0.073 mmol), and P(*O-o*-biph)3 (98 mg, 0. 183 mmol) were added. Argon was purged through the resulting reaction mixture for 0.5 h. A stock solution of Ni(COD)$_2$ in benzene (0.9 mL, 0.07 M) was added and the resulting reaction mixture was irradiated (350 nm, Rayonett chamber) at 50–60 °C. The reaction was monitored by GC. After 2.5 h, 54% of the initial *E*-9 was converted and at this point a 34% yield (63% BORSM)[20] of 8 and 25 (2.5:1 ratio) was obtained (GC). A longer reaction time did not significantly increase the observed yields.

4.7.1. Epoxide 26.
Cyclooctadiene 8 (32 mg, 0. 16 mmol) was dissolved in CH_2Cl_2 (20 mL) and $NaHCO_3$ (34.4 mg, 0.41 mmol) was added. The reaction mixture was cooled to -78 °C, followed by addition of *m*-CPBA (33 mg, 0. 19 mmol). During a period of 1–2 h the reaction was gradually allowed to warm to -20 °C and the epoxide formation was monitored by TLC. When a complete conversion was reached 1 mL triethylamine was added. After stirring for 0.5 h, the reaction mixture was filtered through a plug of SiO_2 (hexane/ethyl acetate). Concentration was followed by flash chromatography (SiO_2, hexane/ethyl acetate = 9:1 (v/v)) yielding epoxide 26 (31 mg, 0.14 mmol, 88%).

^{1}H NMR (300 MHz, CDCl$_3$): δ 5.16 (s, 1H); 5.01 (d, *J*= 1.0 Hz, 1H); 4.93 (s, 1H); 3.0 (br s, 1H); 2.83 (m, 1H); 2.75 (dd, *J*=6.8, 1.8 Hz, 1H); 1.87–2.21 (m, 7H); 1.85 (m, 1H); 1.78 (br s, 6H); 1.69 (ddd, *J*=14.3, 5.5, 3.4 Hz, 1H); 1.04 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 145.5, 134.2, 130.2, 111.7, 64.2, 61.5, 46.1, 38.0, 32.3, 29.6, 27.4, 27.1, 26.5, 24.0, 22.7. IR (thin film): v 3018 (w); 2964 (s); 2938 (s); 2882 (m); 1640 (m); 1493 (m); 1447 (s); 1375 (m); 1239 (w); 1063 (w); 1003 (m) cm^{-1}. HRMS: calcd for $C_{15}H_{22}O$ 218.1670, found 218.1669. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52%; H, 10.16%. Found: C, 82.83%; H, 10.48%.

4.7.2. Salsolene oxide 7.
To a solution of epoxide 26 (24 mg, 0. 11 mmol) in benzene (30 mL) was added [RhCl(PPh$_3$)$_3$] (20 mg, 0.02 mmol). The reaction vessel was saturated with hydrogen by several cycles of evaporation and flushing with hydrogen. The product formation was monitored by GC and filtered through a plug of ALOX III (Et$_2$O). Flash chromatography (SiO_2, hexane/diethyl ether = 9:1 (v/v)) of the crude product gave (±)-salsolene oxide (23 mg, 0.10 mmol, 95%). The spectra are identical to the natural product.[14]

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20. BORSM yield is based on recovered starting material.