

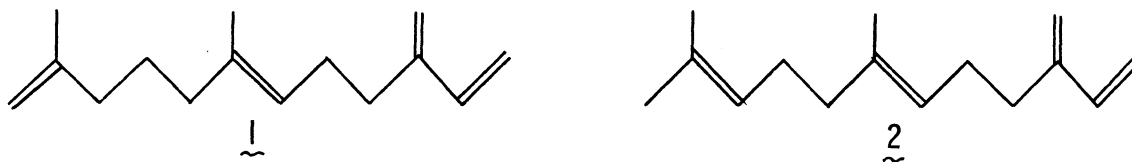
METAL-ASSISTED TERPENOID SYNTHESIS II¹. CATALYTIC CONVERSION OF ISOPRENE INTO FARNESENE AND ITS ISOMER, 2,6-DIMETHYL-10-METHYLENE-1,6-TRANS,11-DODECATRIENE.

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Abstract: A highly selective isoprene trimerization to 2,6-dimethyl-10-methylene-1,6-trans,11-dodecatriene(1) and its double bond isomer, natural β -trans-farnesene (2) was achieved with nickel catalysts. The hydrogen migration pathway crucial for the regio- and stereoselective linear oligomerization was studied to derive a plausible reaction scheme.

In spite of numerous studies on catalytic oligomerization of 1,3-dienes^{3a-e}, only a few linear dimeric oligomers of isoprene may be obtained with reasonable selectivity; for example, 2,7-dimethyl-octatrienes^{4a-e} and 2,6-dimethyl octatrienes^{4b-c,5a-c}. β -Farnesene was reported to have been obtained as a minor product from reactions catalyzed by a composite of nickel naphthenate, PPh_3 and organomagnesium compounds⁶. Catalytic selective synthesis of terpenes based on isoprene is certainly one of the most challenging targets for synthetic chemists. We wish to report here a successful linear trimerization of isoprene to a trimer 1 and β -trans farnesene 2.



General procedures of the reaction solution make-up were as follows: (a) with bis- π -allyl nickel — a hexane solution of $\text{Ni}(\eta^3\text{-C}_3\text{H}_5)_2$ (2.0 mmol) was added to a mixture of ligand (2.0 mmol) and isoprene (100 mmol) at 0°. (b) with π -allyl nickel halide dimer — a hexane solution of $[\text{Ni-Cl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (0.2 mmol) was added to a mixture of ligand (2.0 mmol), alkali alcoholate (2.2 mmol) and isoprene (100 ml) at 0°. (c) with Ziegler type catalyst — a hexane solution of AlEt_3 (0.6 mmol) was added to a mixture of $\text{Ni}(\text{acac})_2$ (2.0 mmol), ligand (2.0 mmol) and isoprene (100 ml)

at -10° . The oligomerization was effected at 50° for 10 hr in sealed tubes. The catalyst having been destroyed with methanol the whole mixture was fractionated under vacuum to give the low-boiling dimer fraction (73–75°/30 mm) and the trimer fraction (81–85°/5 mm) leaving a residue containing tetramers and higher oligomers. Redistillation of the trimer fraction with an efficient column gave 1 in over 95% purity, bp 87°/6 mm. Preparative glc was employed to isolate 2 and the isomer, 2,7,11-trimethyldodeca-1,3,6,11-tetraene(3). Typical results are summarized in Table 1.

The ligand plays a key role in determining the selectivity. With trialkylarsine or amino phosphine such as $\text{PPh}(\text{NEt}_2)_2$ as ligand, the selectivity reaches slightly over 80% when the conversion

Table 1 Nickel-Catalyzed Trimerization of Isoprene ^a

Run	Catalyst Component ^b (mol. ratio)	Conversion(%)	Dimers ^c (%)	Trimers ^d (%)	Residue (%)	Selectivity ^e of (1+2) (%)	Ratio 1/2
1	$\text{Ni}(\eta^3\text{-C}_3\text{H}_5)_2\text{-PPh}(\text{NEt}_2)_2$ (1:1)	35	12	85	3	72	92/8
2	$\text{Ni}(\eta^3\text{-C}_3\text{H}_5)_2\text{-P}(\text{NMe}_2)_3$ (1:1)	32	17	79	4	67	91/9
3	$\text{Ni}(\eta^3\text{-C}_3\text{H}_5)_2\text{-As}(\text{i-Pr})_3$ (1:1)	23	9	89	2	81	93/7
4	$[\text{NiCl}(\eta^3\text{-C}_3\text{H}_5)]_2\text{-PPh}(\text{NEt}_2)_2\text{-Cetyl ONa}$ (1:1:1.2)	25	12	86	2	75	15/85
5	$[\text{NiCl}(\eta^3\text{-C}_3\text{H}_5)]_2\text{-As}(\text{n-Hexyl})_3\text{-t-BuOK}$ (1:1:1.2)	30	10	88	2	77	17/83
6	$\text{Ni}(\text{acac})_2\text{-PPh}(\text{NEt}_2)_2\text{-Et}_3\text{Al}$ (1:1:3)	51	18	77	5	63	90/10
7	$\text{Ni}(\text{acac})_2\text{-PPh}(\text{NEt}_2)_2\text{-Et}_3\text{Al}$ (1:1:3)	55	25	69	6	41	89/11
8	$\text{Ni}(\text{acac})_2\text{-PPh}_3\text{-Et}_3\text{Al}$ (1:1:3)	70	21	73 ^f	6	25	87/13
9	$\text{Ni}(\text{acac})_2\text{-Trimethylolpropane-phosphite-Et}_3\text{Al}$ (1:1:3)	75	15	80 ^g	5	3	—
10	$\text{Ni}(\text{acac})_2\text{-P}(\text{O-o-C}_6\text{H}_5\text{-C}_6\text{H}_4)_3\text{-Et}_3\text{Al}$ (1:1:3)	72	85 ^h	13	2	—	—

a. The reaction was carried out at 50° for 10 hr. b. Two mol% nickel based on isoprene.

c. Dipentene, 1,5-dimethyl-5-vinyl-1-cyclohexene and 1,5-dimethyl cycloocta-1,5-diene.

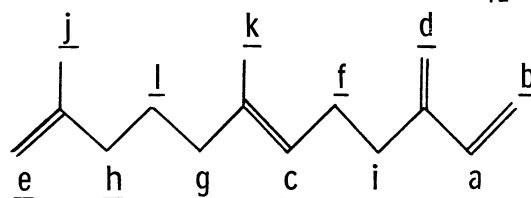
d. linear (1–3) and cyclic (4, 5). e. Based on the reacted isoprene. f. 3 was predominant (41%).

g. cyclic 4 (75%) and 5 (21%). h. 1,5-dimethylcycloocta-1,5-diene (> 92%).

is restricted below 25% (run 1-6 in Table 1). Since the linear trimers are prone to become high boiling products upon prolonged contact with the nickel catalyst, the trimer yield tends to decrease as the conversion proceeds. With PPh_3 , the reaction was faster than that with $\text{PPh}(\text{NEt}_2)_2$, producing a trimer fraction comprized mainly of 3 and two cyclic trimers, namely 1,5,9-trimethyl-(4) and 1,6,9-trimethyl cyclododeca-1,5,9-triene (5) (run 8). Nickel-phosphite catalysts produce mainly cyclic dimers and/or trimers (run 9-10).

2 was identical with natural trans- β -farnesene in the retention time of glc (Golay, R-45), ir, ^1H nmr and mass spectrum⁷. Hence the geometry of the internal double bond of 2, can be deduced to be trans. By comparison of the spectral properties, inter alia, ir and ^1H nmr, we concluded that the internal double bond of 1 is also trans. The ^1H nmr of 1 and dodecadeuterio isomer (1- d_{12}) obtained with 1,1,4,4-tetradeuterioisoprene⁸ under the same condition as run 1 are recorded in Table 2. The coupling constant (1 Hz) of the methyl protons (K) of 1- d_{12} also supports the trans geometry for the internal double bond of 1. The cis isomers of 1 and 2 were not detected in glc.

Table 2 ^1H nmr Spectra of 1 and 1- d_{12} ^a

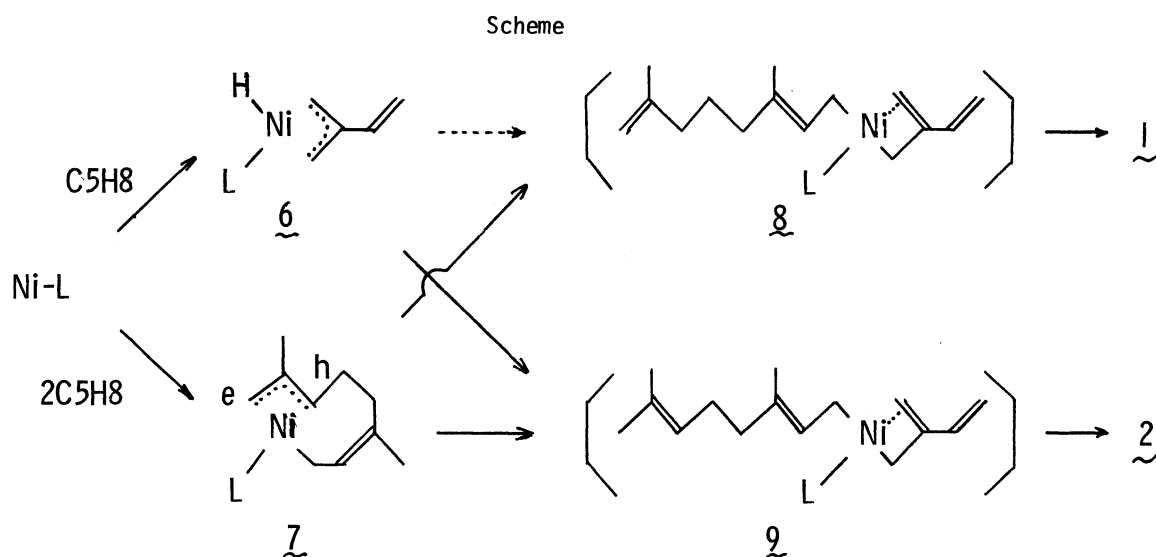


ppm ^b	assignment	intensity	ppm ^b	assignment	intensity ^c
6.27(q)	<u>a</u>	1	6.26(s)	<u>a</u>	1.06
5.10(m)	<u>b,c</u>	3	5.10(s)	<u>b,c</u>	1.09
4.92(s)	<u>s</u>	2	4.90(s)	<u>d</u>	1.78
4.60(s)	<u>e</u>	2			
2.18(m)	<u>f,g</u>	4			
1.90(m)	<u>h,i</u>	4	1.92(s)	<u>h,i</u>	2.09
1.68(s)	<u>j</u>	3	1.64(s)	<u>j</u>	2.98
1.59(s)	<u>k</u>	3	1.54(s)	<u>k</u>	3.00
1.50(m)	<u>l</u>	2			
	total	24		total	12.00

a. JEOL JNM 4H-100, (100 Mc). TMS internal reference. b. Multiplicities are in parenthesis. c. Normalized values.

The deuterium distribution of $\underline{1}$ - \underline{d}_{12} disclosed that 1) the H population at \underline{d} being closer to 2 than to 1, the main hydrogen transfer route is from \underline{d} (the methyl group of the third monomer) to \underline{h} rather than from \underline{i} (the methylene group of the third monomer) to \underline{h} (see Table 2 and Scheme), 2) H-D exchange occurs to a small extent between \underline{d} and \underline{i} , as manifested by the H population (~ 2.1) at sites $\underline{h} + \underline{i}$ and the population (~ 1.8) at site \underline{d} , and 3) H-D scrambling is practically absent at sites \underline{e} , \underline{l} , \underline{g} and \underline{f} . The first and second features are reflected in the ratio $(\underline{h} + \underline{i}/\underline{d})$ which is 1.17 (in the absence of \underline{d} - \underline{i} exchange the ratio should be one).

In order to account for the selective formation of $\underline{1}$ and $\underline{2}$ and hence for the methylene bond formation at 10th position of the trimers, key intermediates $\underline{8}$ and $\underline{9}$ must be postulated. They may be derived from either a hydrido(π -allyl)nickel species $\underline{6}$ or a dimer complex $\underline{7}$. Regioselective consecutive insertion of two molecules of isoprene to Ni-H bond of $\underline{6}$ leads to $\underline{8}$ or $\underline{9}$. Probably, $\underline{9}$ will be produced preferentially from $\underline{6}$ in view of the polarization of isoprene, $\text{CH}_2^{\delta+}=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2^{\delta-}$. Thus, the catalyst system used in run 4 and 5 may favor the formation of $\underline{6}$ rather than $\underline{7}$. The struc-



ture of $\underline{7}$ has been established⁹; the formation requires neither a metal hydride species nor hydrogen transfer. Upon coordination of the third monomer to $\underline{7}$ the methyl hydrogen migrates, presumably first to the metal, then to the π -allylic site \underline{h} or \underline{e} of the dimer ligand in $\underline{7}$, leading to $\underline{8}$ or $\underline{9}$. The formation of the trans internal double bond of the trimer is consistent with the scheme involving an isomerization of the σ -cis-allylic end of the dimer ligand to the σ -trans-allylic end in $\underline{8}$ or $\underline{9}$.

The H-D exchange between \underline{i} and \underline{d} sites suggests occurrence of σ - π valence tautomerism of the allyl coordination in $\underline{6}$, $\underline{8}$ or $\underline{9}$. The key role of the electron donating phosphine ligand L is to

facilitate abstraction of the methyl hydrogen of isoprene upon coordination to the metal owing to the high-oxidation-state-stabilizing property. The Ni-L entity could then serve as a template resulting in the remarkable regio- and stereoselectivities. Electron-accepting phosphite ligands such as $P(O-o-C_6H_5-C_6H_4)_3$ lead to cyclodimerization, as in the case for butadiene oligomerization,^{10,11} a fact accounted for by the low-oxidation-state-stabilizing property. The trimethylolpropanephosphite ligand is characterized by a small steric requirement; it is of interest to observe an efficient cyclotrimerization. Thus, in this case a steric effect is operating in determining the reaction path.

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