



(+)-Limonene (10) is commercially available from Energy Chemical company. It is converted to S-1 in 79% yield using H_2 , PtO_2 , EtOH, rt. S-1 is then converted to 14 in 87% yield using 1. O_3 , DCM, $-78\text{ }^\circ\text{C}$; 2. $TSOH$, MeOH, rt. 14 is converted to 9 using 15. NaH, THF, $70\text{ }^\circ\text{C}$; then LiMe, $-78\text{ }^\circ\text{C}$; then HCl aq., rt. 9 is then converted to 8 using $Zr(n\text{-}PrO)_4$, PhMe; then CH_3ONa , $0\text{ }^\circ\text{C}$. 8 is then converted to 16a using H_2 , Pd/C, THF, rt; then LiHMDS, $PhNTf_2$, $-78\text{ }^\circ\text{C}$ to rt. 16a is then converted to 16b using LiBr, Zn, DMAP, $Ni(OAc)_2 \cdot 4H_2O$, DMF-THF (1:3), rt. 16b is then converted to 15 using MeO^- , Me , $P(=O)(OEt)_2$.

Reference: *J. Am. Chem. Soc.* **1989**, *111*, 6691-6707

E-9 separated
 stereoselective tandem Michael/
 Based on the seminal studies of Stork, Fallis and Ding
 thermodynamically disfavored trans

Synthesis of (-)-Calidoustene

(S)-(-)-3-Methylcyclohexanone (**S-2**)
CAS # 24965-87-5
commercially available from Bide Pharmatech Ltd.

Synthetic Route:

S-2 → **13**: **S-3**, NaH, 90 °C, 92%
aqueous extractive workup then SCC

13 → **18**: 17, Cs₂CO₃, DMSO, rt, 85%, d.r. = 3:1
aqueous extractive workup then SCC

18 → **S-4**: LiHMDS, PhNTf₂, THF; -78 °C to rt, 89%
aqueous extractive workup then SCC

S-4 → **12**: LiCl, Pd(PPh₃)₄, TMSCH₂MgCl, 1,4-dioxane, then NaIO₄, 60 °C, 68%
aqueous extractive workup then SCC

12 → **11**: TMSOTf, Et₃N, DCM, 0 °C to rt, 84%
aqueous extractive workup then SCC
Pummerer/ Sakurai

11 → **S-5**: Na, THF/PrOH (3:1), 55 °C, 53%
aqueous extractive workup then SCC
poly(methylhydrosiloxane) (PMHS) as

S-5 → **20**: IBX, DMSO, rt, 89%
aqueous extractive workup then SCC
competing dimerization of excess Ioa

Reagents and Conditions:

S-3: COC(=O)OC

17: ICCSPH

Reaction Conditions:

S-2 → **13**: **S-3**, NaH, 90 °C, 92%

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18 → **S-4**: LiHMDS, PhNTf₂, THF; -78 °C to rt, 89%

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Table 1. Optimization of the Tandem Pummerer/Sakurai Cyclization^a

Entry	Initiator/Additive	Condition	T (°C)	Yield (%)
1 ^b	Az[2]-I	DCM	0 to rt	0
2 ^c	THAAL	DCM	0 to rt	19
3 ^d	THAAL/DMPA	DCM	0 to rt	19
4 ^e	TMSCOTf/DMPA	DCM	0 to rt	34
5 ^f	TMSCOTf/DMPA	DCM	0 to 60	Disproportion
6 ^g	TMSCOTf/Et ₃ N	DCM	-60 to rt	47
7 ^h	TMSCOTf/Et ₃ N	DCM	0 to rt	84
8 ⁱ	TMSCOTf/Et ₃ N	DCM	0 to rt	0

^aReaction conditions: Initiator (2.0 equiv), Additive (2.0 equiv), 5 mg of compound **12** in 1 mL of DCM. ^bDetermined by ¹H NMR analysis. ^cIncluded yield on 100 mg scale.

competing dimerization of excess 16a

metallaphotoredox-mediated enone

Nozaki-Hiyama-Kishi (NHK) coupling

1. **16a**, CrCl₂, NiCl₂, DMSO, rt.
2. IBX, DMSO, rt, 79% for 2 steps
or
16b, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, NiBr₂·dtbbpy, quinuclidine, K₂CO₃, 1,4-dioxane, rt, 450 nm LEDs, 52%, RSM: 68%

aqueous extractive workup then SCC

MHAT-initiated Baran-Giese radical cyclization

alkene protection

deprotection

poly(methylhydrosiloxane) (PMHS) as

precise stereo-chemical control at

a-hydroxylation-dehydration gave

Reaction conditions: Initiator (2.0 equiv), Additive (2.0 equiv), 0 mg of compound 12 in 0 mL of DCM, Determined by ¹H NMR analysis. *Isolated yield on 300 mg scale.

Entry	Compound	Yield (%)	RSM (%)
1 ^a	Au(I)-	0 to n	0
2 ^b	TBAI-	0 to n	19
3 ^c	TBAI/TBPA	0 to n	19
4 ^d	TMOTC/DMPA	0 to n	34
5 ^e	TMOTC/DMPA	0 to n	40
6 ^f	TMOTC/BzP	-10 to n	47
7 ^g	TMOTC/BzP	0 to n	54
8 ^h	TMOTC/BzP	0 to n	0