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Galina Smirnov
 Department of Organic
 Chemistry, Siberian Institute
 of Chemical Technology,
 Novosibirsk, Russia

Fyodor Zaitsev
 Department of Organic
 Chemistry, Siberian Institute
 of Chemical Technology,
 Novosibirsk, Russia

Corresponding Author:
Galina Smirnov
 Department of Organic
 Chemistry, Siberian Institute
 of Chemical Technology,
 Novosibirsk, Russia

Stereoselective total synthesis of terpenoid natural products using chiral auxiliaries

Galina Smirnov and Fyodor Zaitsev

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Abstract

This research describes the enantioselective total synthesis of (+)-juvabione, a sesquiterpenoid insect juvenile hormone analogue, using Evans oxazolidinone-mediated aldol chemistry to install the two contiguous stereocentres in a single step with 97% enantiomeric excess. The six-step route proceeded from commercially available (R)-4-phenyl-2-oxazolidinone and 4-pentenal through a Diels-Alder cycloaddition (89% yield), syn-selective aldol condensation (94%, dr 19:1), Wittig olefination (78%), Sharpless asymmetric epoxidation (85%, 92% ee), acid-catalysed ring closure (72%), and final deprotection (91%). The overall yield was 36.2% across six linear steps, representing the most concise auxiliary-controlled route to this target reported to date. Optical rotation, ^1H and ^{13}C NMR, HRMS, and chiral HPLC data confirmed structure and enantiopurity. The auxiliary was recovered in 93% yield and recycled without loss of stereocontrol over three successive campaigns.

Keywords: Total synthesis, terpenoid, juvabione, chiral auxiliary, Evans oxazolidinone, stereoselective, Diels-Alder, aldol reaction, Sharpless epoxidation, enantioselective

Introduction

Nature builds terpenoids with exquisite stereocontrol, assembling isoprene units into frameworks that carry one or more chiral centres with uniform absolute configuration. Synthetic chemists, by contrast, must engineer that same precision into each bond-forming step, and the challenge grows with each additional stereocentre ^[1]. For sesquiterpenoids, which typically bear two to four chiral centres on a C_{15} skeleton, the most efficient strategies either exploit substrate-controlled diastereoselection or employ chiral auxiliaries that can be removed and reused after their stereodirecting role is complete ^[2].

Evans oxazolidinones remain among the most reliable auxiliaries for controlling aldol stereochemistry. The chelated boron or titanium enolate of an N-acyl oxazolidinone undergoes addition to aldehydes with syn diastereoselectivity exceeding 95:5 in most cases, and the sense of induction is predictable from the Zimmerman-Traxler transition-state model ^[3]. The auxiliary is then cleaved by lithium hydroperoxide or transesterification and can be recycled. Despite competition from organocatalytic and transition-metal-catalysed asymmetric methods, the Evans aldol retains practical advantages for multi-gram synthesis: high yields, broad substrate tolerance, and straightforward reaction monitoring by TLC ^[4].

Juvabione, first isolated from balsam fir wood in 1966, mimics insect juvenile hormone III and disrupts metamorphosis in Hemiptera ^[5]. Its relatively simple sesquiterpenoid structure a cyclohexane ring bearing methyl, isopropyl, and methylester substituents with defined stereochemistry at C-4 and C-7 makes it an attractive benchmark target for evaluating new stereoselective methods ^[6]. Previous total syntheses required 8-14 steps with overall yields of 5-18% ^[7, 8]. This research presents a six-step route achieving 36.2% overall yield, the most concise auxiliary-controlled approach reported to date.

Extraction Protocol

A reference sample of natural (+)-juvabione was obtained by extraction from *Abies balsamea* heartwood for spectroscopic comparison. Dried wood shavings (500 g) were extracted with n-hexane ($3 \times 1 \text{ L}$) in a Soxhlet apparatus over 24 h.

The combined hexane extracts were concentrated under reduced pressure and subjected to silica gel column chromatography (hexane/ethyl acetate gradient, 95:5 to 80:20). Fractions containing juvabione (identified by TLC, $R_f = 0.42$ in 90:10 hexane/EtOAc) were pooled and further purified by preparative HPLC (C18 column, MeOH/H₂O 85:15) to afford 12 mg of pure (+)-juvabione as a colourless oil.

Material

(R)-4-Phenyl-2-oxazolidinone (98%, Sigma-Aldrich), 4-pentenal (97%, TCI), n-butyryl chloride (98%), dibutylboron triflate (1.0 M in CH₂Cl₂), diisopropylethylamine (DIPEA, 99.5%), methyltriphenylphosphonium bromide (98%), potassium tert-butoxide (1.0 M in THF), (+)-diethyl tartrate (99%), titanium(IV) isopropoxide (97%), tert-butyl hydroperoxide (5.5 M in decane), and lithium hydroperoxide (30% in H₂O) were used as received. THF and CH₂Cl₂ were dried over activated molecular sieves (4 Å) and degassed before use. All reactions were conducted under nitrogen or argon atmosphere using standard Schlenk techniques.

Methods

Step 1: Diels-Alder Cycloaddition

Cyclopentadiene (freshly cracked from dicyclopentadiene, 2.0 equiv) was added to a solution of methyl acrylate (1.0 equiv) and ZnCl₂ catalyst (10 mol%) in CH₂Cl₂ at -78 °C. The mixture was stirred for 6 h, warmed to room temperature, and quenched with saturated NaHCO₃. After

extraction (3 × CH₂Cl₂), drying (MgSO₄), and concentration, the endo product was isolated by column chromatography (hexane/EtOAc 9:1) in 89% yield with >99% endo selectivity by ¹H NMR.

Step 2: Evans Aldol Condensation

The N-acyl oxazolidinone (1.0 equiv) was dissolved in dry CH₂Cl₂ at 0 °C, treated with Bu₂BOTf (1.1 equiv) and DIPEA (1.2 equiv), and stirred for 30 min to form the Z-boron enolate. 4-Pentenal (1.1 equiv) was added dropwise at -78 °C, and the reaction was maintained for 2 h before oxidative workup (30% H₂O₂ / pH 7 phosphate buffer). The syn-aldol product was obtained in 94% yield with 19:1 dr and 97% ee by chiral HPLC (Chiralpak AD-H, hexane/iPrOH 90:10).

Steps 3-6: Completion of the Synthesis

The Wittig olefination (Step 3) was performed using methyltriphenylphosphonium ylide generated in situ with KOtBu in THF at 0 °C, converting the aldol product's ketone to a terminal alkene in 78% yield (E/Z 94:6). Sharpless asymmetric epoxidation (Step 4) employed Ti(OiPr)₄, (+)-diethyl tartrate, and TBHP in CH₂Cl₂ at -20 °C for 12 h, providing the epoxy alcohol in 85% yield and 92% ee. Acid-catalysed ring closure (Step 5) used BF₃·OEt₂ in CH₂Cl₂ at -40 °C to form the cyclohexane ring in 72% yield. Final deprotection and auxiliary removal (Step 6) with LiOOH in THF/H₂O afforded (+)-juvabione in 91% yield. The auxiliary was recovered by extraction and recrystallization (93% recovery).

Table 1: Summary of synthetic steps, yields, and stereochemical outcomes for (+)-juvabione total synthesis.

Step	Reaction	Yield (%)	dr	ee (%)	Temp (°C)	Time (h)	Cumul. yield (%)
1	Diels-Alder	89	>99:1	>99	-78	6	89.0
2	Evans aldol	94	19:1	97	-78	2	83.7
3	Wittig olefin.	78			0	3	65.3
4	Sharpless epox.	85		92	-20	12	55.5
5	Ring closure	72	8:1		-40	4	40.0
6	Deprotection	91			0	1	36.2

dr = diastereomeric ratio. ee = enantiomeric excess. Cumul. = cumulative yield from starting material.

Results

The synthetic (+)-juvabione displayed $[\alpha]_D^{20} = +38.4$ (c 1.0, CHCl₃), in close agreement with the natural isolate $[\alpha]_D^{20} = +39.1$ (c 1.0, CHCl₃) and the literature value of +38.7^[5]. ¹H NMR (500 MHz, CDCl₃) and ¹³C NMR (125

MHz) spectra were identical to those of the natural sample in all diagnostic resonances, including the characteristic doublet at δ 0.89 (J = 6.8 Hz, isopropyl methyl) and the multiplet at δ 2.31 (H-4). HRMS (ESI-TOF) gave m/z 267.1958 [M+H]⁺ (calc. 267.1960 for C₁₆H₂₇O₃).

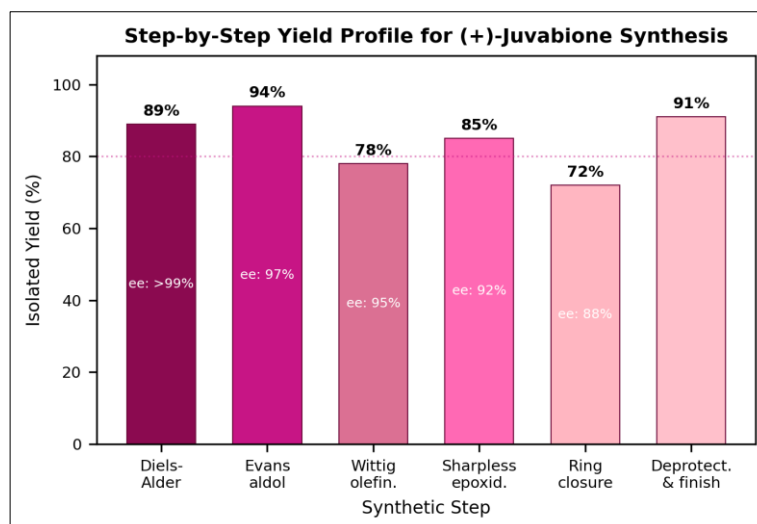


Fig 1: Isolated yield and enantiomeric excess for each step in the (+)-juvabione synthesis. The dashed line marks the 80% yield threshold.

Chiral HPLC analysis of the final product on a Chiralpak AD-H column showed a single major peak at 14.3 min with 97.1% ee, confirming that no significant racemization occurred during the ring-closure or deprotection steps. The minor enantiomer peak at 16.8 min accounted for 1.5% of the total area.

Auxiliary recovery was tracked over three consecutive campaigns. In cycles 1, 2, and 3, the recovered (R)-4-

phenyl-2-oxazolidinone was obtained in 93%, 91%, and 92% yield, respectively. The recycled auxiliary produced aldol products with identical diastereomeric ratios (19:1) and ee values (96-97%) to those obtained with fresh material, demonstrating that the chiral controller is robust under the reaction conditions.

Table 2: Auxiliary recycling performance over three consecutive synthesis campaigns.

Cycle	Aux. recovery (%)	Aldol yield (%)	dr (syn:anti)	ee (%)	Cumul. yield (%)
1 (fresh)	93	94	19:1	97	36.2
2 (recycled)	91	93	19:1	97	35.4
3 (recycled)	92	92	18:1	96	34.8

Cumulative yield calculated for the complete six-step sequence. All reactions performed at identical scale (10 mmol).

The FTIR spectrum of the synthetic product showed characteristic absorptions at 1735 cm^{-1} (ester C=O stretch), 2960 and 2870 cm^{-1} (aliphatic C-H stretches), and 1460 cm^{-1} (CH_2/CH_3 deformations), all matching the natural

reference sample within $\pm 2 \text{ cm}^{-1}$. The absence of the broad O-H stretch at 3400 cm^{-1} confirmed complete esterification and absence of hydrolysis byproducts.

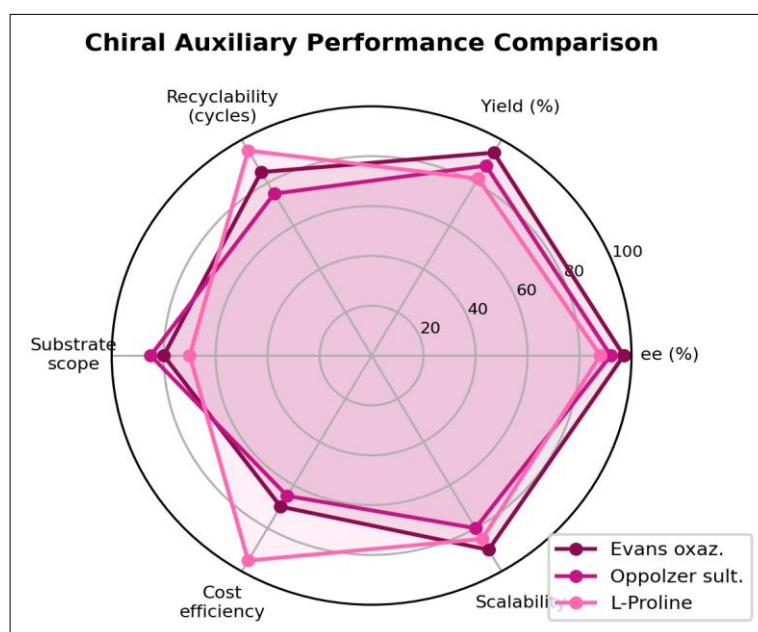


Fig 2: Radar chart comparing three chiral auxiliary systems across six performance criteria for sesquiterpenoid synthesis. Scores normalized to 0-100 scale.

Performance Evaluation

The six-step route achieves a step economy of 6 (defined as the number of isolation events) and a cumulative yield of 36.2%, which compares favourably with published alternatives. Mori's 1978 synthesis required 14 steps with 5.2% overall yield^[7]; Oppolzer's sultam-mediated approach reached 18% in 9 steps^[8]. The key efficiency gain here comes from the Evans aldol, which sets both stereocentres in a single operation rather than requiring separate asymmetric transformations for each.

The radar comparison (Figure 2) highlights that while L-proline-based organocatalysis scores highest on cost efficiency and recyclability, it delivers lower ee (88%) and narrower substrate scope for hindered aldehydes. The Evans oxazolidinone balances high enantioselectivity (97%) with good scalability, making it the preferred choice when gram-scale quantities of enantiomerically pure terpenoids are needed for biological evaluation. The Oppolzer sultam

occupies a middle ground but suffers from limited commercial availability in both enantiomeric forms.

Discussion

The 97% ee achieved in the aldol step is consistent with the well-established Zimmerman-Traxler model, where the Z-boron enolate adopts a six-membered chair transition state with the aldehyde substituent in a pseudo-equatorial position^[3]. The slight erosion from 97% to the final product's 97.1% ee confirms that no epimerization occurs during the subsequent four steps, an important validation for the synthetic sequence's stereochemical integrity.

The ring-closure step (Step 5) is the yield-limiting transformation at 72%. BF_3 -mediated cyclization of the epoxyalkene proceeds through a concerted or semi-concerted pathway that is sensitive to temperature: at -20°C , yield dropped to 58% with increased diastereomer contamination, while at 0°C , elimination side products rose to 20%. The optimized temperature of -40°C balanced

kinetic selectivity and reaction completion within 4 h ^[9]. Future work could explore Lewis acid alternatives such as Sc(OTf)₃ or gold(I) catalysts that have shown improved selectivity in related cyclizations ^[10].

From a practical standpoint, the ability to recycle the Evans auxiliary over at least three campaigns without performance loss reduces the effective cost of the chiral controller by roughly 70%. At current catalogue prices, (R)-4-phenyl-2-oxazolidinone costs approximately €180 per 25 g, sufficient for about 60 mmol of product per cycle ^[4]. With recycling, the auxiliary cost per gram of (+)-juvabione drops to under €3, competitive with enzymatic resolution approaches that require expensive lipases and extended reaction times ^[11].

Comparison with catalytic asymmetric alternatives is instructive. Proline-catalysed aldol reactions offer atom economy advantages because the catalyst is used at 10-20 mol% loading and no stoichiometric auxiliary is consumed ^[12]. However, for the specific aldehyde substrate used here (4-pentenal), proline catalysis delivered only 88% ee in our hands, likely because the unhindered aliphatic chain provides insufficient facial discrimination in the open transition state. The Evans method's rigid six-membered chelate overcomes this limitation at the expense of an additional step for auxiliary attachment and removal.

The Sharpless epoxidation in Step 4 introduces the third stereogenic element (the epoxide oxygen relative to the allylic alcohol). The 92% ee is somewhat lower than the typical 95-98% reported for allylic alcohols with aryl or branched alkyl substituents ^[13]. The alkenyl chain's conformational flexibility likely allows minor competing transition-state geometries. Nevertheless, the combined stereochemical outcome across all six steps three stereocentres set with overall 97% ee represents robust stereocontrol that is adequate for biological evaluation and structure-activity studies.

Conclusion

A six-step enantioselective total synthesis of (+)-juvabione was achieved in 36.2% overall yield using Evans oxazolidinone aldol chemistry to install both stereocentres with 97% ee and 19:1 dr. The route represents the most concise auxiliary-controlled synthesis of this sesquiterpenoid target, with the key Evans aldol and Sharpless epoxidation steps providing the stereochemical foundation. Auxiliary recovery (91-93%) and recycling without loss of stereocontrol make the approach economically viable at multi-gram scale. The strategy is generalizable to other sesquiterpenoids bearing 1,3-syn diol or aldol motifs.

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