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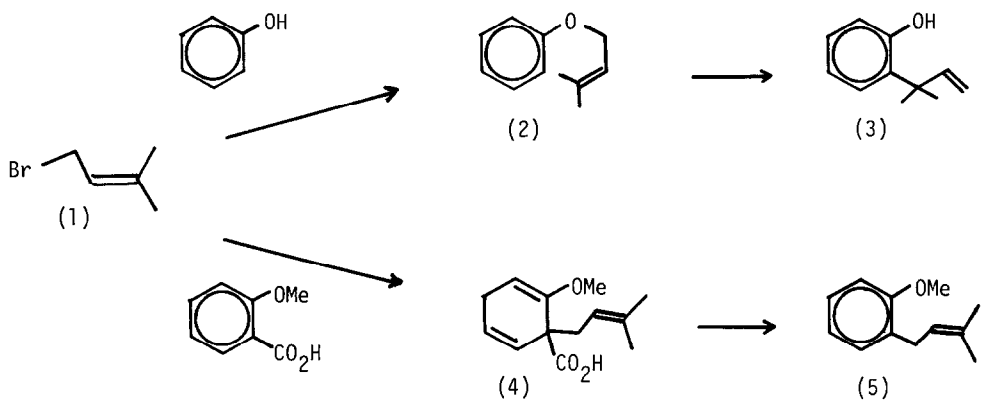
A HYBRID BIRCH-CLAISEN METHODOLOGY FOR ARYLATION AT ALLYLIC TERMINI: SYNTHESIS OF (±)-HERBERTENE

S. Chandrasekaran[1] and John V. Turner*
Research School of Chemistry, Australian National University,
P.O. Box 4, Canberra, A.C.T. 2600, Australia

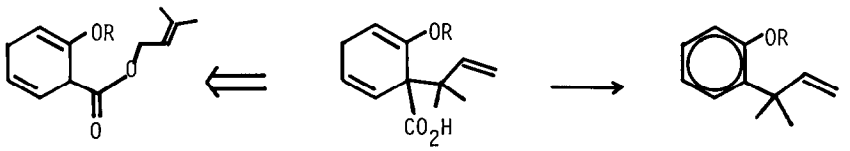
SUMMARY: A hybrid Birch-Claisen methodology has been developed for the regio- and stereo-controlled arylation of allyl groups, and applied to a synthesis of (±)-herbertene.

Regio- and stereo-controlled substitution by an aryl group at one terminus of an allylic substrate is a synthetically important, yet frequently difficult, objective. In recent studies, for example, γ-attack by *alkyl*-copper species on allyl halides could be greatly enhanced with Lewis acids but the regioselectivity of *aryl*-copper reagents could not be improved.[2,3] Alternative, classical, approaches to the problem are the *ortho*-Claisen rearrangement,[4] which generally achieves arylation at the more hindered allylic terminus, e.g. (1) → (2) → (3), and a Birch reductive-alkylation of an aromatic carboxylic acid with an allyl halide, which usually leads to arylation at the less hindered allylic position after oxidative decarboxylation, [5] e.g. (1) → (4) → (5).



However, neither of these regio-complementary arylations works efficiently with allyl groups which are highly substituted or contained within a ring, mainly because regio- and stereochemically controlled syntheses of the required allyl halides is often difficult, and their reaction with phenoxides or carboxy enolates leads to halogen elimination rather than substitution. These, and associated problems, are well exemplified in a recently reported synthesis of (±)-3-hydroxycuparene that features a Claisen rearrangement of an allyl aryl ether.[6]

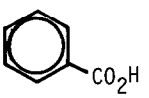
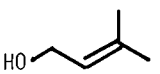
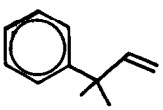
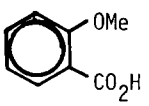
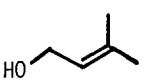
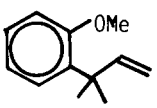
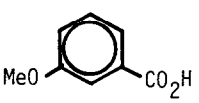
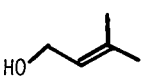
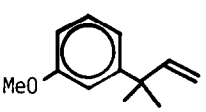
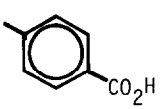
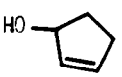
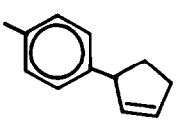
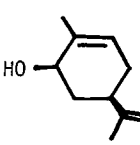
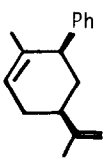
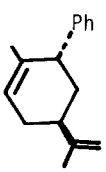
Our interest in sigmatropic rearrangements for making new quaternary and chiral carbon centres[7] has led us to devise a methodology for the arylation of allyl groups that circumvents the above problems and that, moreover, combines the potential of the *ortho*-Claisen rearrangement for regio- and stereo-chemical control, with the superior flexibility of the Birch procedure for combining different aromatic and allylic substrates.



(6) (7) (8)

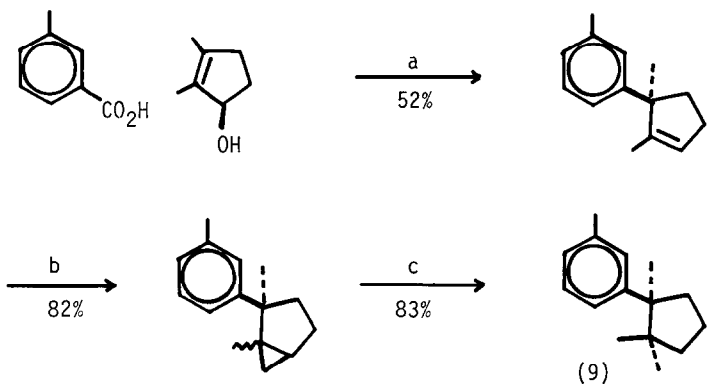
The methodology was founded upon the proposition that an allyl dihydroaromatic acid e.g. (7) [c.f. Birch intermediate (4)] should be accessible from an allylic dihydroaromatic ester[8] (6) through the [3,3]-sigmatropic rearrangement of a silyl ester enolate;[9] oxidative decarboxylation of (7) to (8) [c.f. (4) → (5)] would then establish the equivalence with (3) from the Claisen rearrangement.

TABLE

ENTRY	AROMATIC ACID	ALLYLIC ALCOHOL	PRODUCT	% YIELD OVERALL[10]
1				68
2				61
3				58
4				64
5	$PhCO_2H$	 (-)-*cis*-carveol	 $[\alpha]_D^{20}$ + 506°	49
6	$PhCO_2H$	(-)-*cis*- and (-)-*trans* carveol 7:3	ditto + 7 : 3 	49

This idea has been developed into a General Procedure (below) for regio- and stereo-controlled arylation of allyl groups. The scope can be gauged from the range of examples entered in the Table.[10] Entries 1,2 and 3 serve to illustrate the regio-control of the procedure and its flexibility for different aromatic substrates. Note that, unlike the classical Claisen rearrangement, the formal S_N2' process here is not limited to the generation of *ortho*-substituted phenol derivatives. Entries 4,5 and 6 demonstrate that the methodology is applicable to cyclic allylic substrates. Moreover, Entries 5 and 6 show that the stereochemistry of the resultant C-C bond follows, as expected, from that of the hydroxy group.[9] This allows the chirality at the newly created allylic stereo-centre to be controlled and defined because many strategies are available for obtaining stereochemically, and enantiomerically, pure alcohols.[12]

SCHEME



Conditions

a, General Procedure

b, CH_2I_2, Zn/Cu, Et_2O, Δ, 36 h

c, PtO_2 (10 eq), H_2(1 at) HOAc-NaOAc, 25°, 0.5 h

Finally, the utility of the methodology has been demonstrated by a highly convergent synthesis (see Scheme[10,11]) of (±)-herbertene (9), a recently isolated sesquiterpene.[13,14] The synthesis of the structurally related antibiotic laurinterol using this methodology, and an adaptation for projected syntheses of cytotoxic trichothecanes are in progress.

GENERAL PROCEDURE

Formation of allylic dihydroaromatic esters

1,4-Dihydroaromatic acids were prepared by a Birch reduction[5] in NH_3-THF (4 : 1) and *t*BuOH (1 eq.) at -78° and quenching with NH_4Cl(s) after 20 min. NaH_2PO_4 (10%) was used for acidification on extractive work-up into CH_2Cl_2. The crude dihydro-acid (5 mmol) in dry CH_2Cl_2 (15 ml) at -20° was treated sequentially with Et_3N (1.01 g, 10 mmol), mesyl chloride (537 mg, 5 mmol), and alcohol (5 mmol). After 6 h the ester was isolated from the washed ($NaHCO_3$, 10%),dried (Na_2SO_4) solution.[8] (Note that *ortho*-methoxybenzoic acids in NH_3-THF should be treated with 1 eq. *t*BuOK before normal Birch reduction).

Rearrangement and oxidative decarboxylation

The crude ester (5 mmol) in THF (10 ml) was added to LICA[15] (5.3 mmol) in THF (10 ml) at -78°, Me_3SiCl (572 mg, 5.3 mmol) was added and the mixture warmed to 0° (50° for Entries 5 and 6) during 4.5 h. Acidification with NaH_2PO_4 (10%) gave a crude acid that was oxidatively decarboxylated with $Pb(OAc)_4$ (2.44 g, 5.5 mmol) and $Cu(OAc)_2 \cdot H_2O$ (110 mg, 0.55 mmol) in benzene (12 ml) at 25° for 40 min.[5]

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11. (±)-2,3-Dimethylcyclopent-2-en-1-ol was prepared by DIBAlH reduction of the enone [J.E. McMurry and J. Melton, *J. Org. Chem.*, 38, 4367 (1973)]. Selected data on products from reactions (a) - (c): (a) ^{1}H-NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.45 (s, 3H), 2.24 (s, 3H), 1.2-2.5 (m, 4H), 5.4 (bs, 1H), 6.6-7.2 (m, 4H); HRMS M^+, 186.1410; $C_{14}H_{18}$ calcd M^+ 186.1408. (b) ^{1}H-NMR ($CDCl_3$) δ 0.2-0.65 (m, 3H), 0.86 (s, 3H), 1.28 and 1.32 (2s, 3H, diastereomers), 1.42 (s, 3H), 2.28 (s, 3H), 6.8-7.3 (m, 4H); HRMS M^+, 200.1574; $C_{15}H_{20}$ calcd M^+ 200.1580. (c) ^{1}H-NMR and IR as reported;[13] MS *m/z* 202 (35), 132 (100); HRMS M^+, 202.1736; $C_{15}H_{22}$ calcd M^+ 202.1738.
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