Indian neem tree, *Azadirachta indica* is renowned for its antiseptic, antiviral, antifungal, antibacterial, anti-infertility, antipyretic, anti-inflammatory, anti-ulcer, antihelminthic and insect repellent properties for several thousands of years and is hailed as “Village Pharmacy”, “Divine Tree”, “Heal All”, “Nature’s Drugstore” and “Panacea for all diseases” across many south Asian countries.\(^1\) Crude neem tree extracts have been traditionally used as “eco-friendly” insect repellants, pesticide and fungicide in agriculture across the Indian subcontinent.\(^2\) *Azadirachtin* \(^1\) is a structurally complex natural product first derived from the Indian neem tree in 1968,\(^3\) has remained to be of interest among the organic chemists, biochemists and agro chemists owing to its potent antifeedant and growth-disruptant properties against a broad spectrum of insect species whilst displaying extremely low mammalian toxicity \([\text{LD}_{50} (\text{rat})] > 5 \text{ g/Kg}\) and appears to cause little disruption to beneficial species such as pollinating bees and ladybirds.\(^4\) After several years of intense research the structure of *Azadirachtin* was elucidated in 1987.\(^5\)

For decades the total synthesis of *azadirachtin* \(^1\) has lingered to be a tougher nut to crack, particularly because of the complexity involved in its structure arising from an array of sixteen contiguous stereogenic centres, seven of which are tetrasubsituted along with a diverse assortment of several oxygenated functionalities. Adding to challenges posed by the structural complexity, *azadirachtin* \(^1\) was prone to rearrangement under acidic, basic or photolytic conditions. Also, presence of influential intramolecular hydrogen-bonding interactions, evident from X-ray crystallographis studies,\(^6\) dictated the conformation and reactivity of the *azadirachtin* \(^1\).\(^7\)

The synthesis of *azadirachtin* \(^1\) was pursued simultaneously by several groups in the world including that of Ley,\(^7,8\) Nicolaou,\(^9\) Watanabe.\(^10\) It was only recently Ley’s group overwhelmed the synthesis of *Azadirachtin* \(^1\) via a “Relay Route” protocol.\(^7,8\) This landmark synthesis featured a total of 64 meticulous steps, engaging over 40 synthetic chemists in the Ley group for over 22 years.\(^11\) This problem session will feature analysis of this monumental synthesis from Ley’s group.

**PART-1: A Relay Route for the Synthesis of Azadirachtin 1**

**Scheme 1: Degradation of Azadirachtin 1**

![Synthesis of Azadirachtin via Relay Route](image-url)
Questions for Discussion (for Scheme 1):

(1) What is meant by “Relay Synthesis”? In what way does it differ from the conventional convergent synthesis and diversity-oriented synthesis (DOS)?

(2) In the first step of the degradation of azadirachtin 1, why is the alkene in the dihydrofuran moiety react preferentially with the NBS while the other alkene does not react at all?

(3) Suggest a suitable reagent for step (b).

(4) Discuss why there is selective protection of the hydroxyl groups at C11 and C20 to afford dibenzyl ether 2 [in step (c)]?

(5) Suggest suitable reagents and conditions for steps (d) and (e).

Scheme 2: Return of α-4 and β-4 to Azadirachtin 1

Questions for Discussion (for Scheme 2):

(6) How will you account for the selective debenzylation of OBn group to free alcohol using H₂ gas on Pd/C in methanol [from 4 to 5 in step (b)]. (The authors report that this step was extensively optimised by screening various solvents and varying other experimental conditions without much explanation).

(7) Since the authors successfully achieved the conversion of C23 β epimer of intermediate 5 to azadirachtin 1 in a first generation relay approach, they intended to epimerize the C23 α epimer of the intermediate 5 to the corresponding β epimer. What reagents/conditions could have they used to achieved this? [step (c)]. In this step, the C23 α epimer of the intermediate 5 was successfully epimerised into a 1:1 mixture of diastereoisomers, from which the desired epimer (β-5) was isolated cleanly.

(8) Propose suitable reagents and conditions to effect conversion of β-5 to 6 [three steps - step (d), (e) and (f)]. What will be your order of events?

(9) What is the structure of the intermediate 7?

(10) How is dimethyldioxirane prepared? Give mechanism for the transformation of 7 to the desired natural product azadirachtin 1 [step (i)].
PART-II: Synthesis of the EPIMER β-4

Scheme 3: Retrosynthetic Analysis

Questions for Discussion (for Scheme 4):

(11) The authors synthesized the diol 14 starting from β-D-galactose pentaacetate 13 in three simple steps. Suggest them. Can you also work out an alternative synthesis of the diol 14 starting from simple and commercially available synthons and catalysts.

(12) Taking into consideration of the reagents used in steps (h) – (j) predict the structure of the compound 16. Also, rationalise the reaction mechanism involved in step (h) where NBS is used as the reagent.

(13) What is TPAP? How does NMO act as a co-oxidant during TPAP oxidation? What other co-oxidants will you use instead of NMO?

(14) What are the reactions, reagents and conditions involved in steps (m) and (n)? What are the names of the reactions involved in these steps?

(15) How will you alkylnate the epimers 19 to afford the propargylic mesylate 11 [in three steps (t) – (v)]. [At this stage, the authors had no firm decisions as to whether one or both of these distereoisomers would be brought forward to the natural product. In the end both served as viable precursors (see next section later)].

(16) Imagine if you were involved in the synthesis of the pyran 11, how will you distinguish between the two epimers of 11 by means of physical methods, say by NMR spectroscopic analysis?
Scheme 4: Synthesis of Pyran Fragment 11

MOMCl = Chloromethyl methyl ether; py = pyridine; DMSO = dimethyl sulfoxide; Bn = Benzyl; NBS = N-bromosuccinimide; NMO = N-methyl morpholine-N-oxide; PS = polymer support; DMAP = 4-((N,N-dimethylamino)pyridine; DMF = N,N-dimethyl formamide; TBSCI = tert-butyldimethylsilyl chloride; TMS = trimethylsilyl; PMBTCA = p-methoxybenzyl trichloroacetimidate; DIBAL = diisobutyaluminium hydride; TFA = trifluoroacetic acid.

Questions for Discussion (for Scheme 5):

(17) Why is the addition of Fleming’s dimethyl(phenyl)silylcuprate on to the propargylic acetal 20 stereospecific and regioselective [step (1), Scheme 5]?
(18) What carboxylation reagents and conditions will you suggest for step 2 (Scheme 5) which proceeds soon after the successful addition of the dimethyl(phenyl)silylcuprate on to the propargylic acetal 20?
(19) Propose suitable reagents and conditions for steps (4)-(8) (Scheme 5) in order to obtain the bromo ester 22 from enoate 21.
Questions for Discussion (for Scheme 5) contd.:

(20) What is the role of TMEDA in step (9) involving addition of the anion derived from the dithiane 24 to TBDMS-protected hydroxy aldehyde 23?

(21) While coupling of the alcohol 25 with the bromo ester 22 was attempted using KH as the base [step (10), Scheme 5], the reaction yielded the desired product 27 in 60% yield along with an undesired product 26 (an isomer of 27) in 18% yield. What could be the structure of the undesired compound 26 and outline how could have it be formed?

(22) What is the name of the olefination reaction involved in step (13) and explain the reason for the selectivity observed for the formation of the alkene 29b as the major product from this reaction?

(23) Speculate suitable reagents and conditions for step (14). [The authors did not purify and isolate the product 30 and carried on to the next step (15) directly]

(24) Which of the compounds 31 and 32 are exo and endo product(s) [step (15), Scheme 5]? What are the roles of hydroquinone and DIPEA in this reaction? Rationalise why the intramolecular Diels-Alder reaction of 30 has yielded product 31 as the major product? How can the isomers 31 and 32 be distinguished by NMR spectroscopic analysis?

Scheme 5: Synthesis of Decalin Fragment 12 (part-I):

DMF = N,N-Dimethyl formamide; DIPEA = N,N-diisopropylethylamine
Scheme 6: Synthesis of Decalin Fragment 12 (part II) Contd.:

(16) ?????

(18) ?????

(17) ?????

31 \(\rightarrow\) ?????

33a, 8\%

33b, 45\%

34, 10\%

(19) NaBH₄, MeOH-THF, r.t., 90 min, 82\% of 36, 14\% of 37

35, 81\%

36, 82\%

37, 14\%

(20)-(22) ?????

2 steps from 36

(20)-(21) ?????

3 steps from 37

?????

38

?????

(30) ?????

(31) Zn(BH₄)₂, Et₂O-THF, −10 to −5 °C, 165 min

(32) Cyanoacetic acid, p-toluene sulfonyl chloride, pyridine, CH₂Cl₂, 15 °C, 15 min (93\% over 2 steps)

(33) TBAF, 4 Å sieves, THF, r.t., 15 min, 94\%

(34) PDC, 4 Å sieves, CH₂Cl₂, r.t., 1.5 h, 89\%

(35) ?????

40

41, 82\%

42, 100\%

(36) DMDO, acetone, 0 °C, 22 min

(37) PTPS, MeOH, 5.5 h (70\% over 2 steps)

43. 70\% in two steps. Diastereoisomeric ratio at C11 varied between 4.4:1 to 7:1 in favour of the desired isomer with respect to the natural product depending on reaction time

TFA = Trifluoroacetic acid; PTPS = pyridinium tosate; DMF = N,N-Dimethyl formamide; TBAF = tetra-N-butylammonium fluoride; Å = angstrom; PDC = pyridinium dichromate; DMDO = dimethyldioxirane
Questions for Discussion (for Scheme 6 and 7):

(25) What reagent and conditions can be used for the intramolecular cyclisation of the compound 31 to afford the products 33a, 33b and 34? What is the name of the reaction that is involved in this step [step (16), Scheme 6]?

(26) How is the compound 34 converted to the compound 33b [step (17), Scheme 6]?

(27) Propose two and three step route to 38 from 36 and 37 respectively [steps (20)-(22), Scheme 6].

(28) Explain the protocol involved in step (23) [Scheme 6] where phenyltrialkylsilane 38 is treated with mercury(II) trifluoroacetate with acetic acid and trifluoroacetic acid mixture?

(29) Based on the steps (26) to (29) [Scheme 6], predict the structure of the compound 40.

(30) Propose suitable protocols for step (30) and step (35) [Scheme 6].

(31) Explain the mechanisms involved in steps (36) and (37) [scheme 6] in order to afford the decalin fragment 43 from the cyano lactone 42.

(32) What is the structure of (1S,4R)-Camphanic acid? Name the protocol associated with the step (38) [Scheme 7].

Scheme 7: Synthesis of Decalin Fragment 12 (part III) Contd.:

DMAP = 4-(N,N-Dimethylamino)pyridine; HPLC = high performance liquid chromatography; PTPS = pyridinium tosate; DMF = N,N-Dimethyl formamide; Bn = benzyl
Scheme 8: End Game in the Synthesis of EPIMER β-4 and Azadirachtin 1

**Scheme 8** illustrates the final steps in the synthesis of EPIMER β-4 and Azadirachtin 1. The reaction sequence begins with the coupling of the pyran fragment 11 with the decalin fragment 12 (step (a)). The authors used a ten-fold excess of decalin 12 for complete conversion to propargylic enol ether 10.

**(b)** TBAF, THF, 0 °C, α: 90%, β: 95%

**(c)** Microwave, 1,2-dichlorobenzene, 185 °C, 80%
(or) [(Ph₃PAu)₃O]BF₄, CH₂Cl₂, r.t., 80%

**(d)** TBS-imidazole, DMF, 100 °C, α: 70%, β: 90%

**(e)** DDQ, CH₂Cl₂, H₂O, r.t., 85%

**(f)** CS₂, NaHMDS, THF, -78 °C, then MeI, -78 °C, 60% over 2 steps

**(g)** Bu₃SnH, AIBN, toluene, 100 °C, high dilution, 80%

**(h)** MMPP.H₂O, 5-tert-butyl-4-hydroxy-2-methylphenylsulfide, NaHCO₃, MeOH, 105 °C, sealed tube, 7 days α:20% (85% based on recovered starting material); β:50% (85% based on recovered starting material)

DDQ = Dichlorodicyanoquinone; TBAF = tetra-N-butylammonium fluoride; HMDS = hexamethyldisilazanide; AIBN = azobisisobutyronitrile; TES = triethylsilyl; TBS = tert-butyldimethylsilyl; THF = tetrahydrofuran

Questions for Discussion (for Scheme 8):

(33) How will you couple the pyran fragment 11 with the decalin fragment 12 [step (a), Scheme 8]? The authors used a ten-fold excess of decalin 12 for complete conversion to propargylic enol ether 10.

(34) What type of rearrangement is involved in the conversion of the propargylic enol ether 10 to the allene 47 [Scheme 8]? This rearrangement, which constructs the key C8-C14 bond whilst simultaneously installing the requisite allene, can be induced thermally or by gold(I) catalysed conditions – discuss in detail on the mechanisms involved in this reaction under both conditions.

(35) Give a reasonable mechanism involved in step (g) [Scheme 8] involving tributyltin hydride and AIBN.

(36) What is MMPP [step (h), [Scheme 8]]? Speculate the role of 5-tert-butyl-4-hydroxy-2-methylphenylsulfide in this reaction. The authors quote that this epoxidation reaction of both α- and β-8 yielded the β diastereoisomer of the relay target (β-4), implying an epimerisation of alkene α-8 to its β-8 form prior to epoxidation. This hypothesis was further supported by the observation of the lower yield from the transformation of α-8.
References:

1. (a) http://news.bbc.co.uk/1/hi/world/south_asia/4916044.stm; (b) http://en.wikipedia.org/wiki/Neem

---------Thank you----------

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